Treatment with the Interleukin-17A-Blocking Antibody Secukinumab Does Not Interfere with the Efficacy of Influenza and Meningococcal Vaccinations in Healthy Subjects: Results of an Open-Label, Parallel-Group, Randomized Single-Center Study

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Our objective was to evaluate the efficacy of influenza and meningococcal vaccinations in healthy subjects exposed to the anti-interleukin-17A (IL-17A) monoclonal antibody (MAb) secukinumab. We used an open-label, parallel-group, randomized single-center study of 50 healthy subjects. Subjects received a single 150-mg dose of secukinumab or no treatment, followed by vaccination with inactivated trivalent subunit influenza virus and conjugate group C meningococcal vaccine (Agrippil and Menjugate, respectively) 2 weeks later. Primary efficacy variables were responses of ≥4-fold increases in antibody titer (hemagglutination inhibition [HI]; for influenza virus) and serum bactericidal assay [SBA; for Neisseria meningitidis]) for meningococcus and influenza (at least two out of three serotypes), both at 4 weeks postvaccination. All subjects randomized to secukinumab (n = 25) or the control (n = 25) completed the study. Antibody responses to vaccinations measured at 4 weeks were comparable in both groups, with ≥4-fold increased responses following influenza virus vaccination of 20/25 (80%) for both groups and following meningococcal vaccination of 19/25 (76%) for the secukinumab group and 18/25 (72%) for the control group. Differences between groups were 0% (90% confidence intervals [CI], 19 and 19%) and 4% (90% CI, 16 and 24%) for influenza virus and meningococcal vaccines, respectively. Antibody responses were comparable between the 2 groups at different time points. Headache was the most frequently reported adverse effect. No deaths or serious adverse events were reported. Blockade of IL-17A by secukinumab does not appear to interfere with efficacy of influenza and meningococcal vaccinations, as assessed by the achievement of protective antibody levels. A protective (≥4-fold) immune response to both vaccinations at 4 weeks was achieved in 80 and 76% of subjects exposed to secukinumab and the control, respectively.

Secukinumab is a high-affinity, monoclonal anti-human interleukin-17 (IL-17A) antibody used in clinical trials for immune-mediated inflammatory conditions. IL-17A is produced by memory effector CD4+ and CD8+ T lymphocytes and is a central lymphokine of Th17 cells, which are pivotal for autoimmune inflammatory and immunological processes. In addition, the IL-23-Th17 cell pathway is critical for protective immunity against bacterial and mycotic infections (6). As this compound is being developed for use in a variety of rheumatic conditions (4), it is of interest to determine whether the interference with the IL-17 cytokine could influence the response to antigens and, in general, the measurable response to frequently used vaccinations.

Vaccination against influenza is currently recommended to patients suffering from chronic diseases, including rheumatoid arthritis (RA). Several studies have shown that vaccination against influenza virus is safe with concomitant treatment with biologics and that it induces a satisfactory humoral response, although it may be lower than that in healthy controls (7, 8). Among several commonly used vaccines, the humoral response of patients with RA to vaccination against influenza virus does not seem to be affected by the use of prednisone or disease-modifying antirheumatic drugs (DMARDs), whereas it may be affected by tumor necrosis factor (TNF) blockers.

Recent data (1) with an analog design using canakinumab (Ilaris), a monoclonal antibody against IL-1β, suggest that an interaction with the inflammasome and the IL-1 cascade does not predict a decrease in the efficacy of the vaccines against influenza and meningitis. The current study considered IL-17A as a target that is also involved in the innate immunity cascade.

The rationale of potential interaction between secukinumab and vaccines is based on the generic immunosuppressive potential of monoclonal antibodies targeting T and B cells signaling cytokines, which include TNF antagonists like infliximab, etanercept, and B and T cell-directed agents, like rituximab and abatacept (2). From a clinical viewpoint, the use of biologics for RA and other autoimmune diseases has induced variable effects on vaccination, with rituximab being the only one linked to a detectable decrease in vaccine effectiveness (8). In particular, IL-17-producing CD4+ helper T cells (Th17 cells) have been linked to host defense and autoimmune diseases (9).

The clinical goal that motivated this study was to verify whether this theoretical interference is in play in humans and to what extent, because the literature does not report any attempt to explore the potential interference of IL-17A blockade by securi-
The objective of the present study was to evaluate whether administration of secukinumab affects antibody responses to the commonly used vaccinations that protect against influenza virus and meningococcal infections.

**TABLE 1 Study design scheme and groups**

| Procedure or drug administration on study day: | Group | −14/−1 | 1 | 15 | 21 | 29 | 43 | 57 |
|-----------------------------------------------|-------|--------|---|----|----|----|----|----|
| A (n = 25) Screening | Secukinumab (150 mg) | X | X | X | X | X | X |
| C (n = 25) Screening | MenC + TIV | X | X | X | X | X | X |

| Ab detection | X | X | X | X | X | X | X |

**TABLE 2 Baseline demographic characteristics of the enrolled subjects**

| Characteristic | Secukinumab (n = 25) | Control (n = 25) | All (n = 50) |
|----------------|----------------------|-----------------|--------------|
| Age (yr)       | Means (SD)           | 32.6 (11.52)    | 30.4 (9.46)  |
| Median         | 29.0                 | 30.0            | 29.0         |
| Range          | 18, 55               | 19, 52          | 18, 55       |
| BMI (kg/m²)    | Means (SD)           | 23.49 (2.511)   | 23.54 (2.843) |
| Median         | 23.35                | 22.84           | 23.06        |
| Range          | 19.9, 28.9           | 18.3, 29.0      | 18.3, 29.0   |
| Gender (no. [%]) | Male               | 12 (48)         | 13 (52)      |
| Female         | 13 (52)              | 12 (48)         | 25 (50)      |
| Race (no. [%]) | Caucasian           | 25 (100)        | 24 (96)      |
| Black          | 0                    | 1 (4)           | 1 (2)        |
| Ethnicity (no. [%]) | Mixed ethnicity  | 0               | 1 (4)        |
| Other          | 25 (100)             | 24 (96)         | 49 (98)      |
| Weight (kg)    | Means (SD)           | 67.46 (8.972)   | 68.71 (12.405) |
| Median         | 65.90                | 67.10           | 66.20        |
| Range          | 53.5, 84.6           | 50.3, 98.2      | 50.3, 98.2   |
| Height (cm)    | Mean (SD)            | 169.4 (7.71)    | 170.4 (9.95) |
| Median         | 170.0                | 169.0           | 169.5        |
| Range          | 157, 183             | 157, 194        | 157, 194     |

a TIV, trivalent inactivated influenza vaccine. Subjects in group A were exposed to secukinumab (150 mg s.c.) and then to the vaccines. Subjects in the control group (C) were exposed only to vaccines, and the antibody response was modeled as the normal response. An X indicates that antibody (Ab) titers were obtained at that time point.

Materials and methods

Subjects. Fifty adults out of 122 screened were enrolled in the study.

Main inclusion criteria. Healthy male or female subjects (oral body temperature, 35.0 to 37.5°C; systolic/diastolic blood pressure, 90 to 140/50 to 90 mm Hg; pulse rate, 40 to 90 beats per min), aged between 18 to 55 years (body weight, ≥50 kg; body mass index [BMI], 18 to 29 kg/m²) and with a negative tuberculin skin test reaction (purified protein derivative [PPD], 5 TU; <5-mm induration; 48 to 72 h after administration at the screening visit or within 2 months prior to the screening visit), were included. Subjects who had a positive PPD skin test (as defined by existing guidelines) with a documentation of Mycobacterium bovis BCG vaccination, who were at low environmental risk for tuberculosis infection or reactivation, and who had a negative chest X-ray were also included. Female subjects were required not to be lactating and to have a negative pregnancy test at screening and prior to dosing and were required to use an effective method of contraception (e.g., birth control pills, double-barrier contraception, etc.) during the study (from the date of screening) and for at least 3 months following dosing. Male subjects had to use two acceptable methods of contraception and refrain from fathering a child in the 3 months following study drug administration.

Key exclusion criteria. Exclusion criteria included vaccination of any kind during the preceding year; meningoococal vaccination at any time in the past; influenza virus vaccination in the 2 years prior to screening; allergy to vaccination, investigational compound/class compound, or egg products; active infection; autoimmune or other significant systemic diseases; liver or respiratory diseases; impaired renal function; use of any prescription drugs/herbal supplements within 4 weeks prior to initial dosing; use of over-the-counter (OTC) medication or dietary supplements (vitamins included) within 2 weeks prior to initial dosing; history of drug or alcohol abuse within 12 months prior to dosing; pregnancy; any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs or which might jeopardize study participation.

All subjects provided written informed consent, and the study was conducted in accordance with the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP). The study received approval from the local ethical review committee and health authorities.

Study design. This was a phase 1, single-center, open-label, randomized, parallel-group, single-dose study to evaluate the effectiveness of influenza vaccination and conjugated group C meningococcal (MenC) vaccination following concomitant (~2 weeks) exposure to a single dose of secukinumab (150 mg subcutaneously [s.c.]). A scheme of the study design and the groups is given in Table 1. In this trial, we defined efficacy as the ability of vaccinations to elicit an antibody response, defined as 4 times the baseline titer, at 4 weeks postvaccination for each vaccine in subjects treated with secukinumab compared to the control group.

The primary endpoint was the proportion of subjects with at least a 4-fold increase in titer at 4 weeks postvaccination for meningococcus and in at least 2 out of 3 serotypes for influenza virus. The secondary endpoint was the proportion of subjects showing an increase from a nonprotective baseline level of <1/40 to ≥1/40 in protective antibodies for influenza virus and an increase from <1/8 to ≥1/8 for meningococcus.

The study included a 14-day screening period, and after measurement of antibody titers at baseline, eligible subjects were randomized to a single secukinumab dose (150 mg s.c.) or no treatment (control group), followed by inactivated trivalent subunit unadjuvanted influenza virus
(Agrippal) and conjugated alum-adjuvanted MenC (Menjugate) vaccines given separately intramuscularly in both arms after 2 weeks. The influenza virus vaccine contained 15 μg of hemagglutinin (HA) of the following virus strains: A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain, and B/Brisbane/60/2008. Both vaccines were from Novartis Vaccines and Diagnostics, Siena, Italy. They were sourced locally (H3N2)-like strain, and B/Brisbane/60/2008. Both vaccines were from Novartis Vaccines and Diagnostics, Siena, Italy. They were sourced locally.

Efficacy and safety assessments. The primary efficacy variable was the antibody response to vaccination, defined as ≥4 times the baseline titer, at 4 weeks postvaccination for each vaccine in subjects treated with secukinumab compared to the control group. For influenza virus, response was defined as a ≥4-fold increase in titer postvaccination in at least 2 out of 3 serotypes (there was only one serogroup for meningococcus). Secondary efficacy variables were the antibody responses to vaccination, defined as ≥4 times the baseline titer, at 2 and 6 weeks postvaccination for each vaccine in subjects treated with secukinumab compared to the control group.

Vaccine-specific serum antibody responses were assessed on day 15 (prevaccination) and on days 21, 29, 43, and 57 (1, 2, 4, and 6 weeks postvaccination, respectively). The antibody response to the 3 influenza virus vaccine strains was evaluated by the hemagglutination inhibition (HI; LOQ, titer of 10) test according to standard procedures. The determination of titers was carried out at the Novartis Vaccines and Diagnostics facilities in Marburg (Germany). The antibody response to MenC was evaluated by serum bactericidal assay (SBA; LOQ, titer of 4) using the MenC C11 strain and prescreened human serum as a source of complement. Antibody responses are reported as a 4-fold increase in titer for influenza virus and MenC vaccines and also as rises in antibodies from a nonprotective baseline level of <1/8 to ≥1/8 for MenC compared to the baseline. Geometric mean antibody titers were also calculated for the 3 influenza virus antigens and for MenC.

The safety assessments of treatment with secukinumab consisted of the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), hematology and biochemistry parameters, pregnancy tests, vital signs, and physical examinations.

Statistical analysis. The sample size determination was based on the primary endpoints, i.e., the proportion of subjects with a ≥4-fold increase in antibody titer 4 weeks postvaccination for influenza and meningococcus. With a sample size of 50 subjects (25 subjects per group) for influenza virus vaccination, the study would have 99% power at a one-sided alpha level of 0.05 to establish noninferiority, assuming a control response rate of 87% and a noninferiority margin of 40%. The noninferiority threshold and response rates assumed were similar to those seen in a previous study. The study had an overall power of 87% to demonstrate noninferiority for both vaccinations, assuming there was no real effect of treatment. The difference in proportions of responders in the 2 groups together with 90% confidence intervals (CI) was calculated, and noninferiority was concluded if the lower 90% CI excluded a difference of 40% or more. Efficacy and safety variables were summarized using descriptive statistics.

RESULTS

Characteristics of the enrolled subjects. The 50 enrolled subjects were randomized according to a predetermined code to either the secukinumab group or a control group in a 1:1 ratio (25 subjects per group). The baseline demographics of the enrolled subjects are similar:

| Vaccine, serotype, and group | No. (%) of subjects achieving ≥4-fold increase in titer at postvaccination wk: |
|-----------------------------|---------------------------------|
| **Influenza virus**         |                                 |
| A/California/7/2009 (H1N1)-like strain |                                 |
| Secukinumab                 | 9/25 (36)                       |
| Control                     | 13/25 (52)                      |
| A/Perth/16/2009 (H3N2)-like strain |                                 |
| Secukinumab                 | 4/25 (16)                       |
| Control                     | 7/25 (28)                       |
| B/Brisbane/60/2008          |                                 |
| Secukinumab                 | 3/25 (12)                       |
| Control                     | 9/25 (36)                       |
| **Meningitis**              |                                 |
| MenC (strain C11)           |                                 |
| Secukinumab                 | 8/25 (32)                       |
| Control                     | 10/25 (40)                      |

at a one-sided alpha level of 0.05 to establish noninferiority, assuming a control response rate of 72% and a noninferiority margin of 40%. The noninferiority threshold and response rates assumed were similar to those seen in a previous study. The study had an overall power of 87% to demonstrate noninferiority for both vaccinations, assuming there was no real effect of treatment. The difference in proportions of responders in the 2 groups together with 90% confidence intervals (CI) was calculated, and noninferiority was concluded if the lower 90% CI excluded a difference of 40% or more. Efficacy and safety variables were summarized using descriptive statistics.
presented in Table 2. The groups were similar in demographics and baseline characteristics.

**Efficacy of influenza and meningococcal vaccinations.** Response to influenza vaccination (≥4-fold antibody titer in at least 2 of 3 virus strains) at 4 weeks postvaccination was seen in 20/25 (80%) subjects in both groups (difference in proportions, 0%; 90% CI, −0.19 and 0.19%). Similar response rates across groups were seen at 2 and 6 weeks postvaccination (Fig. 1).

A total of 19/25 (76%) subjects in the secukinumab group showed a ≥4-fold antibody titer in response to MenC vaccination at 4 weeks compared to 18/25 (72%) in the control group (difference in proportions, 4%; 90% CI, −0.16 and 0.24%). Similar response rates were seen at 2 and 6 weeks postvaccination (Fig. 2). The proportion of subjects who had ≥4-fold antibody titers in response to influenza virus and MenC antigen 1, 2, 4, and 6 weeks after vaccination is presented in Table 3, and the proportion of subjects showing ≥4-fold antibody titer response to both influenza virus and MenC vaccination at 4 weeks (primary endpoint) is given in Table 4.

**Antibody protective levels.** The proportions of subjects showing protective levels of antibodies (≥1/40 for influenza virus and ≥1/8 for meningococcus) increased at different study time points from baseline values to comparable values across both secukinumab and control groups (Fig. 3 and 4).

**Levels of antibodies to influenza virus and MenC vaccines.** All of the subjects in the secukinumab and control groups had clinically significant increases in their geometric mean titers of HI antibody against each of the influenza virus antigens tested and of antibody titers against MenC at 2, 4, and 6 weeks postvaccination, with just a small rise at week 1. The antibody titer peaks and persistence over time were comparable between the secukinumab and control groups (Fig. 3). The distribution of peak titer values was similar between the 2 groups, as were the geometric mean titers (Fig. 5).

**Safety and tolerability.** No deaths or serious adverse events occurred during the study. Thirteen (52%) subjects reported at least one AE in the secukinumab group compared to 9 (36%) in the control group. The most commonly reported AEs were headache, injection site pain, and (oro/naso) pharyngitis. Of note, 3 cases of urinary tract infection were reported in the secukinumab group versus none in the control group (Table 5). There were no discontinuations due to AEs in this study.
DISCUSSION

This study evaluated the efficacy of influenza and meningococcal vaccines in healthy subjects exposed to secukinumab, measured as antibody titer rises after unadjuvanted influenza virus and alum-adjuvanted MenC vaccines. Taken together, the data presented here show that treatment with secukinumab does not affect the seroconversion and development of a protective response against influenza virus and against MenC. Indeed, the response to both vaccines was comparable between the secukinumab and control groups. Overall, the response to influenza vaccination showed a marked consistency across the 3 virus strains in healthy subjects in this study, whereas in patients with autoimmune conditions the response can be uneven (3). Most subjects in both the secukinumab and control groups showed a 4-fold antibody titer rise in response to each of the influenza virus strains and MenC at 2, 4, and 6 weeks postvaccination. The steady level of antibodies measured at 6 weeks postvaccination is clinically reassuring given that the response was based on seroconversion in at least 2 out of 3 influenza virus strains.

The results of this study should be considered in the wider context of different biological mechanisms of actions targeting diverse pathways in autoimmune diseases. Previous reports have shown that patients with RA and psoriatic arthritis treated with adalimumab and etanercept were still able to develop an effective response to the tested influenza virus and pneumococcal vaccines (5, 6), whereas other agents, like rituximab, did affect vaccine effectiveness (8). In contrast, the seroconversion rate (defined as ≥4-fold antibody titer) was comparable in the secukinumab and control groups, whereas the rate of protection (using a threshold antibody titer of ≥1:8 for MenC and 1:40 for influenza) was at least 84% at 4 and 6 weeks postvaccination in both groups.

### TABLE 5 Most frequent adverse events observed during the study

| Adverse event                        | Secukinumab (n = 25) | Control (n = 25) | Total (n = 50) |
|--------------------------------------|----------------------|-----------------|---------------|
| Headache                             | 6 (24.0)             | 2 (8.0)         | 8 (16.0)      |
| Injection site pain                  | 3 (12.0)             | 4 (16.0)        | 7 (14.0)      |
| Oropharyngeal pain                   | 1 (4.0)              | 2 (8.0)         | 3 (6.0)       |
| Urinary tract infection              | 3 (12.0)             | 0 (0.0)         | 3 (6.0)       |
| Nasopharyngitis                      | 2 (8.0)              | 0 (0.0)         | 2 (4.0)       |
| Tonsillitis                          | 2 (8.0)              | 0 (0.0)         | 2 (4.0)       |
| Toothache                            | 1 (4.0)              | 1 (4.0)         | 2 (4.0)       |
| Diarrhea                             | 1 (4.0)              | 0 (0.0)         | 1 (2.0)       |
| Fatigue                              | 1 (4.0)              | 0 (0.0)         | 1 (2.0)       |
| Oral herpes                          | 1 (4.0)              | 0 (0.0)         | 1 (2.0)       |
| Procedural pain                      | 1 (4.0)              | 0 (0.0)         | 1 (2.0)       |
| Pyrexia                              | 0 (0.0)              | 1 (4.0)         | 1 (2.0)       |
| Tracheitis                           | 1 (4.0)              | 0 (0.0)         | 1 (2.0)       |
| Vomiting                             | 0 (0.0)              | 1 (4.0)         | 1 (2.0)       |

FIG 5 Ratio (90% CI) of geometric mean titer to the baseline at different study points for both secukinumab and control group serotypes. (A) Serotype A, H1N1; (B) serotype A, H3N2; (C) serotype B; and (D) serogroup C. EOS, end of study.
In conclusion, blockade of IL-17A by secukinumab does not appear to interfere with the efficacy of influenza virus and meningococcal vaccinations, as assessed by the achievement of antibody protective levels after vaccination. A protective (≈4-fold) immune response to influenza and meningococcal vaccinations at 4 weeks was achieved in 80 and 76% of subjects exposed to secukinumab, respectively. This is the first clinical evidence that suggests that in the presence of an anti-IL-17A antibody, vaccination effectiveness with 2 of the most common vaccines in clinical practice is fully preserved and well tolerated.

Further studies may be needed to replicate the results in patients with long-term exposure to secukinumab.

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REFERENCES

1. Chioato A, et al. 2010. Influenza and meningococcal vaccinations are effective in healthy subjects treated with the IL-1 beta blocking antibody, canakinumab: Results of an open-label, parallel group, randomized, single-center study. Clin. Vaccine Immunol. 17:1952–1957.
2. Gelinck LB, et al. 2008. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann. Rheum. Dis. 67:713–716.
3. Hanania NA, et al. 2004. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. J. Allergy Clin. Immunol. 113:717–724.
4. Hueber W, et al. 2010. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci. Transl. Med. 2:52ra72. doi:10.1126/scitranslmed.3001107.
5. Kaine JL, Kivitz AJ, Birbara C, Luo AY. 2007. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J. Rheumatol. 34:272–279.
6. Lin Y, et al. 2009. Interleukin-17 is required for T helper 1 cell immunity and host resistance to the intracellular pathogen Francisella tularensis. Immunity. 31:799–810.
7. National Foundation for Infectious Diseases. 2004. The changing epidemiology of meningococcal disease among U.S. children, adolescents and young adults. National Foundation for Infectious Diseases, Bethesda, MD.
8. Oren S, et al. 2008. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann. Rheum. Dis. 67:937–941.
9. Qian Y, Kang Z, Liu C, Li X. 2010. IL-17 signaling in host defense and inflammatory diseases. Cell Mol. Immunol. 7:328–333.
10. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. 2007. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis Res. Ther. 9:R38. doi: 10.1186/ar2174.