Effect of Secukinumab on Traditional Cardiovascular Risk Factors and Inflammatory Biomarkers: Post Hoc Analyses of Pooled Data Across Three Indications

Joseph F. Merola · Iain B. McInnes · Atul A. Deodhar · Amit K. Dey · Nicholas H. Adamstein · Erhard Quebe-Fehling · Maher Aassi · Michael Peine · Nehal N. Mehta

ABSTRACT

Background: Psoriasis, psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) are chronic immune-mediated inflammatory diseases (IMIDs) associated with cardiovascular (CV) disease. High-sensitivity C-reactive protein (hsCRP) and, more recently, the neutrophil–lymphocyte ratio (NLR) are important inflammatory biomarkers predictive of CV disease and CV disease-associated mortality. Here, we report the effect of interleukin (IL)-17A inhibition with secukinumab on CV risk parameters in patients with psoriasis, PsA, and axSpA over 1 year of treatment.

Methods: This was a post hoc analysis of pooled data from phase 3/4 secukinumab studies in psoriasis, PsA, and axSpA. CV-related exclusion criteria included uncontrolled hypertension and congestive heart failure. Traditional risk factors assessed were body mass index (BMI) > 25, high fasting glucose and blood pressure (systolic and diastolic), and high cholesterol (low-density lipoproteins [LDL], total cholesterol/HDL ratio, and triglycerides). Inflammatory CV risk parameters assessed were hsCRP and NLR. Statistical analysis was descriptive. Subgroup analyses were performed in high-risk patients defined as having baseline hsCRP > 4 mg/L (patients with psoriasis) and > 10 mg/L (patients with PsA/axSpA).

Results: In total, 9197 patients from 19 clinical trials (8 in psoriasis, n = 4742; 5 in PsA, n = 2475; 6 in axSpA, n = 1980) were included. All traditional CV risk parameters remained stable in secukinumab-treated patients through 1 year. Secukinumab rapidly reduced both hsCRP and the NLR compared with placebo at week 12 (psoriasis) or week 16 (PsA/axSpA) in the overall population and in high-risk patients (all P < 0.01). This reduction was maintained for at least 1 year of secukinumab therapy in all indications.
Conclusions: Secukinumab led to a rapid and sustained reduction in hsCRP and the NLR in patients with IMIDs with a high systemic inflammatory burden. Traditional CV risk factors remained stable for at least 1 year in patients with psoriasis, PsA, and axSpA. Taken together, secukinumab had a favorable effect on systemic inflammation without impact on traditional CV risk factors.

Trials Registration: ClinicalTrials.gov, NCT01365455, NCT01358578, NCT01406938, NCT01555125, NCT01636687, NCT02752776, NCT02074982, NCT02826603, NCT01752634, NCT01989468, NCT02294227, NCT02404350, NCT02745080, NCT01863732, NCT01649375, NCT02008916, NCT02159053, NCT02896127, NCT02696031.

Keywords: Axial spondyloarthritis; Cardiovascular; C-reactive protein; Neutrophil–lymphocyte ratio; Psoriasis; Psoriatic arthritis; Secukinumab; Systemic inflammation

INTRODUCTION

Psoriasis, psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) are chronic immune-mediated, systemic inflammatory diseases closely associated with atherosclerotic cardiovascular disease (CV) disease [1–3]. The presence of CV comorbidities in these patients may contribute to increased mortality compared to the general population [1, 4, 5]. Atherosclerosis, which was regarded earlier as a cholesterol storage disease, is now recognized as a chronic immune-mediated inflammatory disease characterized by endothelial dysfunction, lipids deposition in the arterial wall, and infiltration of monocyte-derived macrophages [1]. While classic CV risk factors are prevalent in patients with psoriasis, PsA, and axSpA, these diseases are in themselves independent risk factors for CV disease [1, 3, 6] with which they share key immune pathways and systemic inflammation [1, 7–9]. Atherogenic index was noted to be higher in patients with PsA and axSpA and carotid intima-media thickness was higher in patients with axSpA compared with healthy control patients [2]. Aortic inflammation has been demonstrated in patients with psoriasis, corresponding with elevated levels of the CV risk marker C-reactive protein (CRP) [10]. According to a registry study, traditional CV risk factors and CRP levels were significantly elevated in patients with axSpA compared with healthy control patients [10]. The study also showed that CV risk is associated with increased structural damage as shown by the development of atherosclerotic plaques and increase of carotid intima-media thickness with higher levels of modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and an increased number of syndesmophytes and bone bridges in patients...
with axSpA [3]. A regression analysis in a retrospective cohort of 200 patients with PsA followed for a mean duration of 8.8 years showed that elevated CRP levels were associated with an increased risk of CV events [11]. More recently, the neutrophil–lymphocyte ratio (NLR) has emerged as an inflammatory biomarker that is predictive of CV disease and all-cause mortality [12–14] and is associated with systemic inflammation [15, 16] and coronary artery disease in psoriasis [17]. In patients with psoriasis and axSpA, NLR values are significantly higher versus healthy controls [18, 19]. Biologics therapy can reduce CV events [20, 21], coronary inflammation [22], and high-risk coronary artery plaques [23, 24], and anti-interleukin (IL)-17 therapy had salutary effects on systemic inflammation and coronary plaque burden in patients with psoriasis [24]. An observational study including patients with severe psoriasis who were biologic-naïve at baseline showed that after 1 year of biologic therapy, noncalcified plaque burden decreased by 12% in patients treated with IL-17 inhibitors \( (P < 0.001) \) compared to 5% and 2% with tumor necrosis factor (TNF)-\( \alpha \) inhibitors \( (P = 0.06) \) and anti-IL-12/23 antibody \( (P = 0.36) \), respectively [25].

IL-17A drives neutrophilic inflammation and is proposed as a mechanistic link between psoriasis, PsA, axSpA, and CV disease [8, 9]. Therefore, we explored the effects of secukinumab, a selective IL-17A inhibitor, on systemic inflammation as measured by high-sensitivity C-reactive protein (hsCRP) and the NLR, as well as on traditional CV risk factor parameters in patients across three indications, moderate to severe plaque psoriasis, PsA, and axSpA.

**METHODS**

**Study Design**

This was a post hoc analysis of pooled secukinumab trials in moderate to severe plaque psoriasis (NCT01365455, NCT01358578, NCT01406938, NCT01555125, NCT01636687, NCT02752776, NCT02074982, NCT02826603), PsA (NCT01752634, NCT01989468, NCT02294227, NCT02404350, NCT02745080), and axSpA (NCT01863732, NCT01649375, NCT02008916, NCT02159053, NCT02896127, NCT02696031). All patients in these trials had data for CV risk factor parameters and inflammatory biomarkers at baseline and after receiving treatment. Here, 1-year data are reported in patients treated with 150 or 300 mg secukinumab. Control data from the placebo arms up to week 12 in psoriasis and week 16 in PsA and axSpA are reported for comparison. CV disease-related exclusion criteria from study protocols included uncontrolled hypertension and congestive heart failure. All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All studies were approved by all competent ethics committees and regulatory authorities. Informed consent was obtained by investigators from all patients enrolled into these studies.

**Study Outcomes**

Traditional CV risk parameters reported were body mass index (BMI), fasting plasma glucose, blood pressure (systolic and diastolic), cholesterol (high- and low-density lipoproteins [HDL/LDL] and total cholesterol/HDL ratio), and lipids (apolipoprotein A1/B and fasting triglycerides). Inflammation-associated CV risk parameters reported were hsCRP and NLR (ratio of absolute neutrophil and lymphocyte counts). Study outcomes were presented side by side for all three indications: psoriasis, PsA, and axSpA.

Time points included were baseline and weeks 12 (psoriasis)/16 (PsA/axSpA) for comparison of primary outcomes with placebo. The 24- and 52-week timepoints were exploratory to understand the potential durable impact on these parameters following crossover. hsCRP and NLR were also analyzed in a high-risk subgroup (baseline hsCRP > 4 mg/L in the psoriasis cohort and > 10 mg/L in PsA and axSpA cohorts). The rationale for selecting a higher hsCRP cutoff for PsA/axSpA high-risk subgroups was based on higher hsCRP levels in these patients reported to be associated with CV risk [26, 27] than in patients with psoriasis [28].
Statistical Analysis

Statistical analysis was descriptive. Exploratory statistical comparison of secukinumab versus placebo for change from baseline in hsCRP and NLR to week 12 (psoriasis) and week 16 (PsA and axSpA) using Wilcoxon two-sample test was carried out post hoc. Nominal two-sided P values derived from testing equality of distributions are provided and can be interpreted as assessing the difference in the medians of the two distributions.

RESULTS

Study Population

This analysis comprised more than 9000 patients, including 4742 patients from the secukinumab psoriasis, 2475 patients from the PsA, and 1980 patients from the axSpA programs. Of these patients, 26.5% (psoriasis) had baseline hsCRP > 4 mg/L, while 25.5% (PsA) and 35.9% (axSpA) had baseline hsCRP > 10 mg/L. Table 1 demonstrates baseline demographics by indications and treatment group. In the psoriasis group, 53.6% of the overall population had at least one CV comorbidity of any type; 38.3% were obese (BMI ≥ 30 kg/m²) at baseline. In the PsA and axSpA groups, 41.2% and 21.8% had obesity (BMI ≥ 30 kg/m²) at baseline, respectively. Time since first diagnosis of psoriasis, PsA, and axSpA was 17.9, 6.5, and 6.5 years, respectively. Disease activity at baseline was comparable between the three treatment groups, secukinumab 150 mg or 300 mg and placebo, in all indications (psoriasis, PsA, and axSpA). Overall, the mean psoriasis area and severity index (PASI) score was 21.6 (psoriasis), mean tender joint count (TJC)-78, swollen joint count (SJC)-76, and disease activity score-28 (DAS28)-CRP scores were 20.9, 10.7, and 4.6, respectively (PsA), and the mean bath ankylosing spondylitis disease activity index (BASDAI) score was 6.9 (axSpA). All baseline cardiovascular risk parameters were comparable between treatment groups within each indication but differed from one indication to another. Compared with psoriasis and PsA, patients with axSpA had lower median serum fasting glucose, LDL cholesterol, ratio of total cholesterol/HDL, and triglyceride levels at baseline (Table 2). Median BMI, systolic and diastolic BP, and apolipoprotein levels were comparable in patients with psoriasis, PsA, and axSpA.

In patients with psoriasis, PsA, or axSpA, median CRP and NLR values at baseline were comparable between the secukinumab and placebo arms. Compared with psoriasis, both the PsA and axSpA cohorts showed higher CRP values at baseline, while NLR was comparable in all cohorts of patients (Table 3).

Traditional Cardiovascular Risk Factor Parameters Remain Stable in Patients on Secukinumab Treatment

Serum fasting glucose, systolic and diastolic blood pressure, and BMI were comparable between the secukinumab 150 mg or 300 mg arm versus placebo at week 12 in patients with psoriasis, and week 16 in patients with PsA and axSpA. Likewise, all lipid parameters were comparable between secukinumab and placebo at week 12/16 in patients with psoriasis, PsA, and axSpA. Generally, all traditional CV risk parameters remained stable in secukinumab-treated patients in all indications through week 52 (Table 2, Figs. 1, 2). No difference of impact on CV risk factors was observed between the 150 mg and 300 mg dose of secukinumab.

Secukinumab Decreased High-Sensitivity C-Reactive Protein and the Neutrophil Lymphocyte Ratio in a Rapid and Sustained Manner

Secukinumab significantly reduced both hsCRP and NLR median values compared with placebo as early as week 12 (psoriasis cohort) or week 16 (PsA/axSpA cohorts), and this effect was sustained with secukinumab through week 52 (Fig. 3a, c). In the overall psoriasis population, in which hsCRP was modestly elevated at baseline, hsCRP was slightly reduced by secukinumab from baseline to week 12 compared to placebo, while in the subgroup with high
|                  | Psoriasis | PsA        | axSpA       |
|------------------|-----------|------------|-------------|
|                  | SEC 150 mg| SEC 300 mg | PBO         | SEC 150 mg| SEC 300 mg| PBO         |
|                  | N = 765   | N = 3285   | N = 692     | N = 1177  | N = 76    | N = 727     |
| Age (years), mean ± SD | 45.4 ± 13.54 | 44.9 ± 13.73 | 44.7 ± 12.79 | 48.8 ± 12.11 | 48.5 ± 12.58 | 49.3 ± 12.27 |
| Gender, n (%)     |           |            |             | 39.4 ± 11.61 | 42.1 ± 11.81 | 40.1 ± 12.32 |
| Female            | 232 (30.3) | 1089 (33.2) | 208 (30.1)  | 462 (50.9)  | 453 (51.1)  | 377 (55.4)  |
| Male              | 533 (69.7) | 2196 (66.8) | 484 (69.9)  | 445 (49.1)  | 434 (48.9)  | 304 (44.6)  |
| Race, n (%)       |           |            |             | 755 (64.1)  | 50 (65.8)   | 479 (65.9)  |
| White             | 558 (72.9) | 2836 (86.3) | 509 (73.6)  | 805 (88.8)  | 814 (91.8)  | 615 (90.3)  |
| Asian             | 142 (18.6) | 237 (7.2)   | 121 (17.5)  | 65 (7.2)    | 45 (5.1)    | 38 (5.6)    |
| Black or African American | 14 (1.8) | 40 (1.2)   | 13 (1.9)    | 0 (0.0)     | 5 (0.6)      | 5 (0.7)     |
| American Indian or Alaska Native | 33 (4.3) | 64 (1.9) | 28 (4.0) | 11 (1.2) | 1 (0.1) | 2 (0.3) |
| Others*           | 18 (2.3) | 108 (3.3) | 21 (3.0) | 26 (2.8) | 22 (2.5) | 21 (3.1) |
| Current smoking, n (%) | 280 (36.6) | 1183 (36.0) | 230 (33.2) | 199 (21.9) | 183 (20.6) | 131 (19.2) |

*axSpA* axial spondyloarthritis, *PBO* placebo, *PsA* psoriatic arthritis, *SD* standard deviation, *SEC* secukinumab

*Includes Native Hawaiian or other Pacific Islander, other, or unknown
| Table 2: Traditional CV risk factors over 52 weeks |
|-----------------------------------------------|
| **Median (Q1, Q3)** | **Psoriasis** | **PsA** | **axSpA** |
|                  | SEC | SEC | PBO | SEC | SEC | PBO | SEC | SEC | PBO | SEC | SEC | PBO |
|                  | 150 mg | N = 765 | 300 mg | N = 3285 | N = 907 | 300 mg | N = 887 | N = 681 | 150 mg | N = 1177 | 300 mg | N = 76 |
| Serum fasting glucose (mmol/L) | 5.2 (4.77, 5.72) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.72, 5.70) | 5.2 (4.70, 5.70) | 5.2 (4.70, 5.70) | 5.2 (4.70, 5.70) | 5.2 (4.70, 5.70) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) |
| Baseline | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Week 12 | 5.3 (4.80, 5.80) | 5.2 (4.80, 5.70) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) | 5.3 (4.80, 5.70) |
| Week 16 | NA | NA | 5.2 (4.90, 5.80) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) | 5.2 (4.80, 5.70) |
| Week 24 | 5.2 (4.83, 5.80) | 5.3 (4.90, 5.80) | NA | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) | 5.3 (4.80, 5.80) |
| Week 52 | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | NA | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) | 5.2 (4.80, 5.80) |
| Systolic blood pressure (mmHg) | 127.0 (119.00, 138.00) | 128.0 (120.00, 138.00) | 126.0 (118.00, 136.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) | 128.0 (120.00, 138.00) |
| Baseline | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Week 12 | 125.0 (118.00, 135.00) | 127.0 (119.00, 137.00) | 125.0 (117.00, 134.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) | 127.0 (119.00, 137.00) |
| Week 16 | 125.0 (117.00, 134.00) | 127.0 (118.00, 136.00) | 125.0 (117.00, 134.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) | 128.0 (118.00, 136.00) |
| Week 24 | 125.0 (116.00, 134.00) | 127.0 (119.00, 137.00) | NA | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) | 127.0 (120.00, 136.00) |
| Week 52 | 126.0 (118.00, 135.00) | 127.0 (119.00, 136.00) | NA | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) | 126.5 (119.00, 136.00) |
|                              | Psoriasis | PsA      | axSpA    |
|------------------------------|-----------|----------|----------|
|                              | SEC 150 mg| SEC 300 mg| PBO N = 692 | SEC 150 mg| SEC 300 mg| PBO N = 681 | SEC N = 727 |
| Diastolic blood pressure (mmHg) | Baseline | 80.0 (74.00, 86.50) | 80.0 (74.00, 86.00) | 80.0 (74.00, 86.00) | 80.0 (71.00, 84.00) | 80.0 (71.50, 85.00) | 79.0 (71.00, 84.00) |
|                              | Week 12   | 80.0 (75.00, 88.00) | 80.0 (73.00, 84.00) | 80.0 (74.00, 84.00) | 78.0 (71.00, 80.00) | 80.0 (72.00, 84.00) | 78.0 (70.00, 83.00) |
|                              | Week 16   | 80.0 (73.00, 87.00) | 79.0 (72.00, 84.00) | 80.0 (73.00, 84.00) | 80.0 (72.00, 84.00) | 78.0 (72.00, 84.00) | 83.00 |
|                              | Week 24   | 80.0 (73.00, 87.00) | NA | 80.0 (73.00, 84.00) | 78.0 (71.00, 84.00) | 80.0 (74.00, 84.00) | NA |
|                              | Week 52   | 80.0 (75.00, 87.00) | NA | 80.0 (73.00, 84.00) | 77.0 (70.00, 83.00) | 80.0 (74.00, 84.00) | NA |
| Body mass index (kg/m²)      | Baseline  | 28.4 (24.70, 33.10) | 27.9 (24.49, 32.30) | 27.8 (24.50, 32.10) | 29.1 (25.00, 33.36) | 28.1 (24.84, 32.33) | 28.7 (25.21, 32.99) |
|                              | Week 12   | 28.7 (24.90, 33.20) | 28.3 (24.50, 33.20) | 27.8 (24.30, 32.20) | 29.1 (25.00, 33.36) | 28.1 (24.84, 32.33) | 28.7 (25.21, 32.99) |
|                              | Week 16   | NA | 27.8 (24.59, 32.00) | 35.3 (35.30, 35.30) | 28.7 (25.06, 32.89) | 27.9 (24.94, 31.99) | 28.5 (25.26, 32.77) |
|                              | Week 24   | 28.5 (24.90, 32.70) | NA | 29.2 (25.33, 33.52) | 28.5 (25.46, 32.75) | 25.8 (22.70, 29.41) | 27.4 (24.44, 31.40) |
|                              | Week 52   | 28.6 (25.00, 32.80) | NA | 29.3 (25.29, 33.17) | 28.3 (24.61, 32.41) | 25.7 (22.68, 29.36) | 27.9 (25.28, 31.41) |
| Table 2 continued |
|-------------------|
| **Median (Q1, Q3)** | **Psoriasis** | **PsA** | **axSpA** |
| | **SEC 150 mg** | **SEC 300 mg** | **PBO** | **SEC 150 mg** | **SEC 300 mg** | **PBO** | **SEC** | **SEC** | **PBO** |
| | **N = 765** | **N = 3285** | **N = 692** | **N = 907** | **N = 887** | **N = 681** | **N = 1177** | **N = 76** | **N = 727** |
| **Total cholesterol** | 5.0 (4.25, 5.66) | 4.9 (4.32, 5.62) | 5.0 (4.34, 5.80) | 5.0 (4.34, 5.72) | 5.0 (4.33, 5.61) | 5.0 (4.44, 5.82) | 4.7 (3.98, 5.46) | 4.8 (4.06, 5.15) | 4.6 (4.03, 5.41) |
| (mmol/L) | | 5.0 (4.33, 5.79) | 4.9 (4.29, 5.70) | 5.0 (4.27, 5.70) | NA | 4.9 (4.30, 5.57) | NA | NA | NA |
| **Week 12** | NA | 5.0 (4.35, 5.69) | 5.1 (4.39, 5.78) | 5.1 (4.37, 5.72) | 5.0 (4.40, 5.60) | 4.7 (4.07, 5.51) | 4.7 (4.23, 5.31) | 4.7 (4.00, 5.31) |
| **Week 24** | 5.0 (4.35, 5.75) | 4.9 (4.27, 5.66) | NA | 5.1 (4.38, 5.84) | 5.2 (4.37, 5.71) | 4.7 (4.01, 5.47) | 4.9 (4.28, 5.37) | NA |
| **Week 52** | 5.1 (4.35, 5.75) | 4.9 (4.29, 5.65) | NA | 5.1 (4.37, 5.76) | 4.9 (4.35, 5.68) | 4.7 (4.06, 5.46) | 4.7 (4.17, 5.32) | NA |
| **HDL cholesterol** | 1.2 (1.01, 1.48) | 1.3 (1.09, 1.59) | 1.2 (1.04, 1.48) | 1.4 (1.12, 1.70) | 1.4 (1.17, 1.72) | 1.4 (1.14, 1.62) | 1.3 (1.12, 1.54) | 1.4 (1.11, 1.63) |
| (mmol/L) | | 1.2 (0.98, 1.50) | 1.2 (1.03, 1.48) | NA | 1.4 (1.17, 1.74) | NA | NA | NA |
| **Week 12** | NA | 1.4 (1.14, 1.66) | NA | 1.4 (1.13, 1.70) | 1.4 (1.12, 1.68) | 1.4 (1.13, 1.66) | 1.4 (1.15, 1.66) | 1.3 (1.15, 1.55) |
| **Week 16** | 1.2 (1.01, 1.50) | 1.2 (1.01, 1.50) | NA | 1.4 (1.14, 1.70) | 1.4 (1.18, 1.74) | 1.3 (1.09, 1.59) | 1.4 (1.17, 1.55) | NA |
| **Week 24** | 1.2 (1.01, 1.50) | 1.3 (1.09, 1.61) | NA | 1.4 (1.13, 1.68) | 1.4 (1.16, 1.69) | 1.4 (1.16, 1.66) | 1.3 (1.11, 1.56) | NA |
| **Week 52** | | | | | | | | |
|                | Psoriasis | PsA | axSpA |
|----------------|-----------|-----|-------|
|                | SEC 150 mg | SEC 300 mg | PBO N = 692 | SEC 150 mg | SEC 300 mg | PBO N = 681 | SEC 150 mg | SEC 300 mg | PBO N = 727 |
| **LDL cholesterol (mmol/L)** | | | | |
| Baseline       | 3.1 (2.52, 3.80) | 3.1 (2.52, 3.68) | 3.1 (2.54, 3.83) | 3.1 (2.53, 3.74) | 3.1 (2.58, 3.68) | 3.1 (2.60, 3.72) | 2.9 (2.37, 3.58) | 3.0 (2.30, 3.39) | 2.9 (2.34, 3.50) |
| Week 12        | 3.2 (2.54, 3.80) | 3.1 (2.51, 3.75) | 3.1 (2.51, 3.80) | NA | 3.1 (2.51, 3.67) | NA | NA | NA | NA |
| Week 16        | NA | 3.2 (2.61, 3.77) | NA | 3.2 (2.56, 3.73) | 3.1 (2.56, 3.73) | 3.1 (2.55, 3.64) | 2.9 (2.40, 3.63) | 2.9 (2.52, 3.29) | 2.9 (2.29, 3.47) |
| Week 24        | 3.2 (2.53, 3.81) | 3.1 (2.51, 3.73) | NA | 3.2 (2.58, 3.78) | 3.1 (2.56, 3.75) | NA | 2.9 (2.35, 3.51) | 3.0 (2.49, 3.40) | NA |
| Week 52        | 3.2 (2.58, 3.79) | 3.1 (2.57, 3.76) | NA | 3.2 (2.61, 3.76) | 3.1 (2.56, 3.79) | NA | 3.0 (2.41, 3.60) | 2.8 (2.38, 3.38) | NA |
| **Ratio of total cholesterol/HDL** | | | | |
| Baseline       | 4.0 (3.26, 4.94) | 3.9 (3.09, 4.95) | 4.1 (3.15, 4.93) | 3.6 (2.90, 4.44) | 3.4 (2.76, 4.28) | 3.6 (2.88, 4.31) | 3.4 (2.75, 4.17) | 3.4 (2.85, 4.37) | 3.4 (2.73, 4.19) |
| Week 12        | 4.0 (3.26, 5.15) | 4.0 (3.12, 5.02) | 4.0 (3.17, 4.95) | NA | 3.3 (2.71, 4.20) | NA | NA | NA | NA |
| Week 16        | NA | NA | NA | 3.6 (2.91, 4.58) | 3.6 (2.92, 4.46) | 3.6 (2.95, 4.33) | 3.4 (2.70, 4.15) | 3.4 (2.91, 4.43) | 3.4 (2.73, 4.17) |
| Week 24        | 4.1 (3.27, 5.03) | 4.0 (3.11, 4.96) | NA | 3.7 (2.91, 4.59) | 3.4 (2.80, 4.37) | NA | 3.5 (2.83, 4.32) | 3.4 (2.89, 4.17) | NA |
| Week 52        | 4.1 (3.29, 5.15) | 4.0 (3.12, 4.83) | NA | 3.6 (2.94, 4.56) | 3.5 (2.82, 4.35) | NA | 3.3 (2.69, 4.10) | 3.4 (2.85, 4.16) | NA |
|                                    | Psoriasis | PsA | axSpA |
|------------------------------------|-----------|-----|-------|
|                                    | SEC 150 mg| SEC 300 mg | PBO |
|                                    | N = 765   | N = 3285 | N = 692 |
|                                    | SEC 150 mg| SEC 300 mg | PBO |
|                                    | N = 907   | N = 887 | N = 681 |
|                                    | SEC 150 mg| SEC 300 mg | PBO |
|                                    | N = 1177  | N = 76 | N = 727 |
| Triglycerides (mmol/L)             | Baseline  |       |       |
| Week 12                            | 1.5 (1.06, 2.26) | 1.4 (0.99, 2.10) | 1.4 (0.96, 2.08) |
| Week 24                            | 1.5 (1.07, 2.29) | 1.4 (1.01, 2.10) | NA |
| Week 52                            | 1.6 (1.10, 2.37) | 1.4 (0.95, 1.99) | NA |
| Apolipoprotein A1 (g/L)            | Baseline  |       |       |
| Week 12                            | 1.4 (1.21, 1.62) | 1.4 (1.23, 1.61) | 1.4 (1.24, 1.63) |
| Week 16                            | 1.4 (1.21, 1.62) | NA | NA |
| Week 24                            | 1.4 (1.25, 1.62) | NA | NA |
| Week 52                            | 1.4 (1.25, 1.63) | NA | NA |
Table 2 continued

| Median (Q1, Q3) | Psoriasis | PsA | axSpA |
|-----------------|-----------|-----|-------|
|                 | SEC 150 mg | SEC 300 mg | PBO |
| Secukinumab 150 mg | N = 765    | N = 3285 | N = 692 |
| Apolipoprotein B (g/L) | Baseline | 1.0 (0.84, 1.20) | 1.0 (0.83, 1.20) | 1.0 (0.85, 1.17) | 1.0 (0.84, 1.14) | 1.0 (0.85, 1.15) | 0.9 (0.78, 1.13) | 0.9 (0.74, 1.03) | 0.9 (0.77, 1.11) |
| Week 12 | 1.0 (0.82, 1.22) | 1.0 (0.82, 1.19) | 1.0 (0.81, 1.21) | NA | NA | NA | NA | NA | NA |
| Week 16 | NA | NA | NA | 1.0 (0.87, 1.20) | 1.0 (0.84, 1.19) | 1.0 (0.84, 1.17) | 0.9 (0.79, 1.13) | 0.9 (0.77, 1.03) | 0.9 (0.77, 1.09) |
| Week 24 | 1.0 (0.82, 1.19) | 1.0 (0.82, 1.18) | NA | 1.0 (0.86, 1.20) | 1.0 (0.84, 1.20) | NA | 0.9 (0.77, 1.11) | 0.9 (0.80, 1.08) | NA |
| Week 52 | 1.1 (0.87, 1.24) | 1.0 (0.84, 1.20) | NA | 1.0 (0.88, 1.22) | 1.0 (0.86, 1.18) | NA | 1.0 (0.80, 1.15) | 0.9 (0.78, 1.10) | NA |

Baseline is defined as the last observation on the day of or before the first dose of study drug. Data are reported "as observed" in patients with baseline value and at least one post-baseline value.

axSpA: axial spondyloarthritis, CV: cardiovascular, HDL: high-density lipoprotein, LDL: low-density lipoprotein, PBO: placebo, PsA: psoriatic arthritis, SEC: secukinumab.
Table 3 Median change from baseline in hsCRP and NLR with secukinumab

| Median change from baseline (Q1, Q3) | Psoriasis | PsA | axSpA |
|-------------------------------------|-----------|-----|-------|
|                                     | SEC       | PBO | SEC   | PBO   | SEC   | PBO   |
| 150 mg N = 765                      | 2.6 (1.10, 5.90) | 2.3 (1.10, 4.90) | 25.0 (1.05, 5.45) | 4.2 (1.70, 9.80) | 4.6 (1.80, 10.90) | 4.4 (1.80, 9.95) | 6.2 (2.40, 14.50) | 6.8 (1.90, 12.80) | 6.0 (2.40, 14.10) |
| 300 mg N = 3285                     | 2.3 (1.10, 4.90) | 2.1 (1.00, 3.43) | 2.6 (1.00, 3.88) | 4.4 (1.70, 9.80) | 4.6 (1.80, 10.90) | 4.6 (1.80, 9.95) | 6.2 (2.40, 14.50) | 6.8 (1.90, 12.80) | 6.0 (2.40, 14.10) |

Overall population

| hsCRP (mg/L) | NCRP | P = 0.001 | NCRP | P = 0.001 | NCRP | P = 0.001 |
|--------------|-------|-----------|-------|-----------|-------|-----------|
| Baseline     | 2.6 (1.10, 5.90) | 2.3 (1.10, 4.90) | 25.0 (1.05, 5.45) | 4.2 (1.70, 9.80) | 4.6 (1.80, 10.90) | 4.4 (1.80, 9.95) | 6.2 (2.40, 14.50) | 6.8 (1.90, 12.80) | 6.0 (2.40, 14.10) |
| Week 12/16*  | -0.4  | -0.3      | -0.1  | -0.8      | -1.4  | 0.0       | -2.1  | -2.1      | -0.2 |
| (-2.10, 0.30)| (-2.00, 0.30)| (-1.00, 0.80)| (-5.00, 0.20)| (-6.20, 0.10)| (-2.00, 1.80)| (-8.80, 0.00)| (-9.50, 0.20)| (-3.00, 1.70)|
| P < 0.001    | P < 0.001 | P < 0.001 | P < 0.001 | P < 0.001 |

NLR

| hsCRP (mg/L) | NCRP | P = 0.001 | NCRP | P = 0.001 | NCRP | P = 0.001 |
|--------------|-------|-----------|-------|-----------|-------|-----------|
| Baseline     | 2.5 (1.86, 3.45) | 3.2 (2.49, 3.21) | 2.6 (2.01, 3.33) | 2.6 (1.94, 3.46) | 2.6 (1.95, 3.38) | 2.5 (1.93, 3.33) | 2.5 (1.88, 3.30) | 2.2 (1.82, 3.13) | 2.5 (1.93, 3.25) |
| Week 12/16*  | -0.4  | -0.7      | -0.1  | -0.4      | -0.5  | 0.0       | -0.4  | -0.5      | 0.0 |
| (-1.00, 0.14)| (-1.42, -0.08)| (-0.56, 0.38)| (-1.01, 0.16)| (-0.97, 0.09)| (-0.97, 0.49)| (-0.97, 0.18)| (-1.08, 0.19)| (-0.58, 0.50)|
| P < 0.001    | P < 0.001 | P < 0.001 | P < 0.001 | P = 0.0011 |

High-risk patients subgroup (baseline hsCRP > 10 mg/L in PsA/axSpA and > 4 mg/L in psoriasis)

| hsCRP (mg/L) | NCRP | P = 0.001 | NCRP | P = 0.001 | NCRP | P = 0.001 |
|--------------|-------|-----------|-------|-----------|-------|-----------|
| Baseline     | 8.0 (5.60, 14.05) | 7.3 (5.30, 13.40) | 8.7 (5.40, 16.50) | 19.9 (14.90, 41.30) | 17.5 (13.70, 35.30) | 17.9 (12.80, 40.20) | 19.6 (13.45, 42.30) | 16.6 (11.80, 35.15) | 23.3 (13.00, 46.30) |
| Week 12/16*  | -3.2  | -3.3      | 1.8   | -14.7     | -13.2 | -4.1      | -13.7 | -12.9     | -4.6 |
| (-8.00, -0.80)| (-8.95, -0.90)| (-5.40, 1.60)| (-33.00, -7.30)| (-29.80, -7.90)| (-14.80, 4.10)| (-32.20, -7.80)| (-27.60, -8.80)| (-11.90, 1.00)|
| P = 0.001    | P = 0.0002 | P < 0.0001 | P < 0.0001 | P < 0.0001 |

NLR

| hsCRP (mg/L) | NCRP | P = 0.001 | NCRP | P = 0.001 | NCRP | P = 0.001 |
|--------------|-------|-----------|-------|-----------|-------|-----------|
| Baseline     | 2.9 (2.16, 4.03) | 2.8 (2.13, 3.68) | 3.0 (2.30, 4.01) | 3.3 (2.60, 4.31) | 3.0 (2.43, 3.92) | 3.1 (2.21, 3.94) | 3.0 (2.23, 3.84) | 2.7 (2.08, 3.96) | 2.9 (2.18, 3.69) |
systemic inflammation (baseline hsCRP [4 mg/L]), secukinumab markedly reduced median hsCRP from baseline to week 12 (Fig. 3a, Table 3). This reduction was sustained over 1 year of treatment in the overall population (−0.3 mg/L each with secukinumab 150 and 300 mg) and the high-risk subgroup (−3.4 and −3.0 mg/L with secukinumab 150 and 300 mg, respectively). Despite the PsA and axSpA cohorts having baseline hsCRP levels higher than the psoriasis cohort, a similar trend of improvement was observed across these indications. Compared with placebo, secukinumab significantly reduced hsCRP from baseline to week 16 in the overall PsA/axSpA population, with even better improvements noted in the high-risk (hsCRP > 10 mg/L at baseline) subgroup (Fig. 3b, c, Table 3). As in psoriasis, these improvements were sustained with secukinumab 150 and 300 mg over 1 year of treatment in the overall PsA (−0.8 and −1.4 mg/L) and axSpA populations (−3.4 and −3.0 mg/L, respectively). Despite the PsA and axSpA cohorts having baseline hsCRP levels higher than the psoriasis cohort, a similar trend of improvement was observed across these indications.

In patients with psoriasis, the median NLR decreased significantly with secukinumab versus placebo from baseline to week 12 (Fig. 3a, Table 3). High hsCRP (> 4 mg/L) at baseline was noted in the high-risk (hsCRP > 10 mg/L) at baseline to week 16 in the overall PsA/axSpA population, with even better improvements with secukinumab 150 and 300 mg and the high-risk subgroup (−3.4 and −3.0 mg/L, respectively). Despite the PsA and axSpA cohorts having baseline hsCRP levels higher than the psoriasis cohort, a similar trend of improvement was observed across these indications.
sustained over 5 years of treatment while the traditional CV risk factors did not change (Supplementary Tables 1 and 2).

**DISCUSSION**

Systemic inflammation and lipid dysmetabolism in psoriatic disease are associated with an increased risk of cardiometabolic disease. Several studies in psoriasis and psoriatic arthritis have demonstrated the presence of elevated systemic and vascular inflammation in patients with psoriasis using $[^{18}F]$fluorodeoxyglucose positron emission tomography–computed tomography as well as coronary computed tomography [10, 22]. In the present study, secukinumab treatment led to significant reductions in hsCRP and NLR, both predictors of CV disease and mortality [12, 13]. Both markers decreased rapidly and were maintained thereafter under secukinumab treatment throughout the observation period. This was consistently noted across three indications—psoriasis, PsA, and axSpA. Secukinumab did not adversely affect traditional CV risk factors as previously has been shown [6, 29].

The effect of treatment with biologics on CV-related risk factors in patients with psoriasis has been inconsistent, with some studies demonstrating a positive effect and others reporting no change. TNFα inhibitors, the most commonly used biologics to treat psoriasis, have been demonstrated to be successful reducers of systemic inflammation including NLR; however, the role of TNFα inhibitors in reducing CV risk is still debated given that they increase apolipoprotein B as well as being associated with weight gain. Some studies demonstrate a positive effect [30–34] or no effect [35–39] of TNF inhibitors on CV risk and mortality. A recent review reported that TNF inhibitors have a beneficial effect on endothelial function and markers of arteriosclerosis; however, whether this benefit is translated into CV risk reduction remains to be answered in focused clinical trials [40]. Results from a randomized, placebo-controlled study on ustekinumab, an IL-12/IL-23 inhibitor, showed that it transiently reduces aortic vascular inflammation in patients with psoriasis over 12 weeks; however, this effect was not sustained over 52 weeks [41]. In a similarly designed study, secukinumab did not significantly reduce aortic vascular inflammation compared with placebo. However, a beneficial effect was seen in patients with high baseline vascular inflammation showing a significant reduction in aortic vascular inflammation from baseline to week 12, although it was not replicated in patients who switched from placebo to secukinumab from week 12 to 52 [42].

Anti-IL-17 therapy was recently shown to reduce coronary inflammation [23], decrease coronary artery plaque burden [23], and reduce

![Fig. 1](https://via.placeholder.com/150)

**Fig. 1** Median BMI and total cholesterol/HDL with secukinumab over 52 weeks. **BMI** body mass index, **HDL** high-density lipoproteins
lipid-rich necrotic core [24] following 1 year of therapy. Additionally, previous long-term safety analysis demonstrated a low exposure-adjusted incidence rate (< 1/100 patient-years) of major adverse CV events across same indications in secukinumab-treated patients [43]. Furthermore, in a randomized study in patients with psoriasis, impaired endothelial function at
Fig. 3 Effect of secukinumab on inflammatory CV risk parameters in the overall population and the high-risk subgroup over 52 weeks. Data presented as median. \*P < 0.0001, \^P < 0.001, \$P < 0.05. P values for comparison between secukinumab 150 mg or 300 mg versus placebo based on Wilcoxon two-sample test for changes from baseline to week 12 (psoriasis)/week 16 (PsA and axSpA). CV cardiovascular.
baseline, as measured by flow-mediated dilation, was modestly restored after 52 weeks of secukinumab treatment [44]. In another study, anti-IL-17 therapy showed ameliorations in arterial intima-media thickness after 6 months of treatment in patients with severe psoriasis, suggesting a potential beneficial effect of anti-IL-17 therapy on cardiovascular complications of systemic inflammation [45]. Secukinumab decreased hsCRP levels over 52 weeks in patients with psoriasis [46]. Correspondingly, our present data demonstrate that secukinumab efficiently reduced hsCRP, particularly in high-risk patients with baseline hsCRP > 4 mg/L in psoriasis and > 10 mg/L in the PsA/axSpA cohorts. Levels of hsCRP were reduced below the cutoff for high CV risk (> 3 mg/L) [47] at week 12 (psoriasis) and week 16 (PsA/axSpA) in the overall population, and the response was sustained over 1 year. Collectively, these results suggest that the CV risk, in patients across psoriasis, PsA, and axSpA indications, may decrease following secukinumab treatment and that patients with high systemic inflammation may particularly benefit from anti-IL-17 therapy. Notably, the reduction of inflammatory CV risk markers in the 150 mg secukinumab arm was as pronounced as in the 300 mg arm.

Neutralization of IL-1β was shown to reduce major adverse CV events in certain high-risk patients, a proof of principle that targeting systemic inflammation can reduce CV risk while reducing hsCRP and the NLR [14, 21]. To bridge the gap of our present findings from biomarkers to clinical outcomes, larger dedicated randomized trials are needed.

IL-17A is thought to mechanistically link psoriasis, PsA, and axSpA pathogenesis, neutrophil recruitment, and atherosclerosis [8, 9, 48, 49]. The proatherogenic effect of IL-17A is caused by the increased production of other cytokines, chemokines, and matrix metalloproteinases and the recruitment of immune cells, particularly neutrophils. IL-17 also induces apoptosis of endothelial cells and cardiomyocytes by activating caspase-3 and caspase-9, and upregulating the Bax/Bcl-2 ratio [49]. Together with the present study this suggests that targeting IL-17A may directly reduce neutrophil-mediated CV inflammation in patients with psoriasis. A recent analysis of over 60,000 patients demonstrated that the NLR predicted CV risk and all-cause mortality, and that anti-inflammatory therapy could reduce the NLR in patients with a history of CV disease [14]. An NLR ≥ 2.15 in an African-American population predicted increased all-cause mortality in patients with CV disease [12], and an NLR > 2.29 was associated with an increased non-calcified coronary artery burden (NCB) [17] in patients with psoriasis. In this study, the overall psoriasis, PsA, and axSpA populations had median NLR values between 2.4 and 2.6 at baseline, indicating that a large proportion of them were at high CV risk. Following secukinumab treatment, the median NLR was stabilized at approximately 2.0, even in patients with baseline hsCRP > 4 mg/L (psoriasis) or > 10 mg/L (PsA and axSpA), and remained within the physiological range as reported in healthy subjects [50]. In a recent study, 1 year of biologic therapy was associated with a 14.5% decrease in the NLR and with a change in NCB [17]. Our data extend these findings, suggesting stable protective effects even in patients with high systemic inflammation.

Statistical interpretation of these data should be made with caution since the tests were performed post hoc, without predefined hypothesis, and no multiplicity adjustment was made. A further limitation of these analyses is that potential heterogeneity resulting from pooling of different studies cannot be excluded.

**CONCLUSION**

Our analyses show that in patients with chronic systemic inflammation, secukinumab did not alter traditional CV risk factor parameters in psoriasis, PsA, or axSpA. Treatment with secukinumab was associated with a reduction in hsCRP and the NLR, two important markers of systemic inflammation and CV risk. While dedicated randomized clinical trials are still needed to validate these findings across long-term clinical outcomes, these findings may be useful to inform management of patients with psoriatic and rheumatic diseases, with concomitant CV risks or comorbidities.
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Compliance with Ethics Guidelines All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All studies were approved by all competent ethics committees and regulatory authorities. Informed consent was obtained by investigators from all patients enrolled into these studies.

Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due to their scope (i.e., the datasets of 19 Novartis-sponsored clinical studies across three indications were analyzed).

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