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Associations Between Safety of Certolizumab Pegol, Disease Activity, and Patient Characteristics, Including Corticosteroid Use and Body Mass Index

Vivian P. Bykerk,[1] Andrew Blauvelt,[2] Jeffrey R. Curtis,[3] Cécile Gaujoux-Viala,[4] Tore K. Kvien,[5] Kevin Winthrop,[6] Nicola Tilt,[7] Christina Popova,[7] Xavier Mariette,[8] and Boulos Haraoui[9]

Objective. To investigate the impact of baseline and time-varying factors on the risk of serious adverse events (SAEs) in patients during long-term certolizumab pegol (CZP) treatment.

Methods. Safety data were pooled across 34 CZP clinical trials in rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and plaque psoriasis (PSO). Cox proportional hazards modeling was used to investigate the association of baseline patient characteristics with risk of serious infectious events (SIEs), malignancies, and major adverse cardiac events (MACEs). Cox modeling for recurrent events assessed the impact of time-varying body mass index (BMI), systemic corticosteroid (CS) use, and disease activity on SIE risk in RA and SAE risk in PSO.

Results. Data were pooled from 8747 CZP-treated patients across indications. Cox models reported a 44% increase in SIE risk associated with a baseline BMI of 35 kg/m^2 or more versus a baseline BMI of 18.5 kg/m^2 to less than 25 kg/m^2. Baseline systemic CS use, age of 65 years or more, and disease duration of 10 years or longer also increased SIE risk. Older age was the only identified risk factor for malignancies. The risk of MACEs increased 107% for BMI of 35 kg/m^2 or more versus BMI of 18.5 kg/m^2 to less than 25 kg/m^2 and increased 51% for men versus women. Higher disease activity, older age, systemic CS use, BMI of 35 kg/m^2 or more, and baseline comorbidities were SIE risk factors in RA. Age and systemic CS use were risk factors for SAEs in PSO.

Conclusion. Age, BMI, systemic CS use, and disease activity were identified as SIE risk factors in CZP-treated patients. Risk of malignancies was greater in older patients, whereas obesity and male sex were MACE risk factors.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are chronic conditions in which normal immune responses are dysregulated, leading to a high comorbidity burden and increased susceptibility to adverse events (AEs) compared with the general population (1). For example, patients with rheumatoid arthritis (RA) have a comparatively higher risk of infections (2), and patients with psoriasis (PSO) are more likely to develop metabolic syndrome–associated comorbidities, including obesity and cardiovascular disease, compared with the general population (3,4). RA, axial spondyloarthritis (axSpA), and psoriatic arthritis (PsA) have also been associated

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SIGNIFICANCE & INNOVATIONS

- There is limited information on the influence of underlying disease activity and characteristics of patients with chronic inflammatory disease on the safety profile of biologic treatments. This study used long-term data from certolizumab pegol (CZP) clinical trials (representing more than 17 000 patient-years' total CZP exposure across indications) to examine the impact of disease activity and specific patient characteristics on the risk of serious adverse events over time.
- Age, body mass index, and systemic corticosteroid use were risk factors for serious infectious events (SIEs) across approved indications. As expected, risk of malignancies was greater in older patients, whereas obesity and male sex were identified as risk factors for major adverse cardiac events.
- Cox modeling including time-varying covariates demonstrated that a reduction in rheumatoid arthritis disease activity significantly reduced the risk of SIEs, suggesting that good disease management may lead to fewer infections.
- These results suggest that specific patient characteristics should be taken into account in clinical decision-making and that the benefits of high-level disease control not only include improved functionality but also extend to patient safety.

with a comparatively elevated risk of cardiovascular disease (5–7). The risk of such AEs may increase with higher disease activity (8–10), body mass index (BMI) (11–13), older age, and systemic corticosteroid (CS) use (14–17) in addition to comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), and osteoporosis (14,17–20).

Examining the risk of specific AEs in patients with IMIDs during long-term exposure to immunomodulator medications may help physicians to identify specific risk factors for different patient subpopulations and distinguish study drug effects from disease-associated events. Although the benefit–risk profile of anti-tumor necrosis factor (TNF) agents is well established (21–30), information on the impact of specific patient characteristics on the safety profile of anti-TNF agents and other biologics remains limited. A better understanding of these factors may help clinicians counsel patients regarding the risk of specific AEs during treatment and help set expectations to facilitate shared decision-making.

Certolizumab pegol (CZP), an Fc free, PEGylated anti-TNF agent, is approved for treatment of RA, axSpA (ankylosing spondylitis and nonradiographic axSpA), PsA, PSO, and Crohn disease. A recent safety update demonstrated that, across indications, the CZP safety profile is consistent with other anti-TNF medications (24). Here, we examined the influence of baseline demographic and disease-related factors on the risk of serious AEs (SAEs), including serious infectious events (SIEs), malignancies, and major adverse cardiovascular events (MACEs), in CZP-treated patients with RA, PsA, axSpA, and PSO. In addition, we used large data sets in RA and PSO to determine the impact of time-varying factors such as disease activity on SIE and SAE risk, respectively.

PATIENTS AND METHODS

Data sources and patient populations. Safety data were pooled across 34 CZP clinical trials comprising 27 in RA, one in axSpA, one in PsA, and five in PSO, a subset of those described in the recently published CZP long-term safety update (24). Data cut offs were April 2016 for axSpA and PsA data, August 2017 for RA data, and August 2017 for PSO data (Supplemental Figures S1–S3). For time-varying PSO analyses, data were assessed for all patients receiving one or more doses of CZP up to 144 weeks of exposure and prior to completion of the phase 3 studies (CIMPASI-1 [NCT02326298]: October 2018; CIMPASI-2 [NCT02326272]: September 2018; and CIMPACT [NCT02346240]: December 2018). When study design included patients switching between another anti-TNF agent and CZP (EXXELERATE [NCT01500278] in RA and CIMPACT in PSO; Supplementary Figure S1 and S3) (31,32), only events occurring during CZP treatment in patients originally randomized to CZP were included (ie, data were censored at the time of switch to adalimumab in EXXELERATE, and patients originally randomized to etanercept in CIMPACT were excluded).

Briefly, eligibility criteria for inclusion in these trials included age of 18 years or more; active disease; a clinical diagnosis made 6 months or more before study enrollment; inadequate response to or intolerance of at least one nonsteroidal anti-inflammatory drug. Exclusion criteria included evidence of chronic or clinically significant infections (including active or latent tuberculosis); history of or current malignancy or congestive heart failure; history of or suspected demyelinating disease of the central nervous system; and previous exposure to more than two biologics or more than one TNF inhibitor. Patients were also excluded if they were breastfeeding, pregnant, or planning to become pregnant within 3 months of the last dose of study drug. Studies were conducted across central/eastern and western Europe, Asia, Japan, North America, and Latin America.

Safety assessments. SAEs were recorded and categorized according to the Medical Dictionary for Regulatory Activities version 18.1. SAEs were broadly defined as medical occurrences that were life threatening; led to death, hospitalization, congenital

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anomalies or birth defects, or persistent or significant disability; or were considered serious by the study investigator. Infections requiring treatment with intravenous antibiotics were also classified as serious.

SAEs of potential concern included SIEs, malignancies, and MACEs that occurred between the first CZP dose and 70 days or fewer after the last CZP dose, study withdrawal, or death. All malignancies, including nonmelanoma skin cancers (NMSCs), were included. MACEs included fatal and nonfatal myocardial infarction, serious cerebrovascular events, and serious congestive heart failure. All SAEs of potential concern were medically reviewed by an external expert committee using predefined case rules described in detail elsewhere (24). Venous thromboembolism events (VTEs) were considered but could not be included in the analyses, as there were very few events (24).

Observed incidence rates (IRs) with 95% confidence intervals (CIs) were calculated as the number of first occurrences of an SAE per 100 patient-years (PY). For the Cox proportional hazards models (described below), patients were censored at the time of the first event of interest.

Cox proportional hazards models. *Baseline risk models.* Three Cox proportional hazards models were used to estimate the hazard ratio (HR) of time to first SIE, malignancy, or MACE across indications. Baseline covariates included age (<45 yr, 45 yr to <65 yr, and ≥65 yr), sex (male or female), disease duration (<1 yr, 1 to <5 yr, 5 to<10 yr, and ≥10 yr), methotrexate (MTX) use (yes or no), prior anti-TNF drug use (yes or no), BMI category (<18.5 kg/m^2, 18.5 kg/m^2 to <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, 30 kg/m^2 to <35 kg/m^2, and ≥35 kg/m^2), and systemic CS use (yes or no). Models were adjusted based on RA as a reference indication, as it represented the largest patient cohort in the analysis data set (n = 6927). A stepwise selection procedure was implemented to produce the final reduced models (a probability of 0.25 was used for entry into and retention in the model). As patient medical history was not readily accessible for the pooled safety analyses, baseline comorbidities were not included in the baseline models. Covariates used in each Cox model were retained if $P \leq 0.25$; covariates with $P \leq 0.05$ were identified as risk factors.

Time-varying risk models. To account for specific comorbidities and the time-varying nature of disease activity, separate recurrent event Cox models were built for RA and PSO. It was not possible to develop similar models for PsA and axSpA because of the limited numbers of patients and SAEs reported. The RA model examined time-varying SIE risk (the most frequent type of SAE) using data from the RAPID (Rheumatoid Arthritis Prevention of Structural Damage) 1 (NCT00152386) and RAPID2 (NCT00160602) studies and their respective open-label extensions (NCT00175877 and NCT00160641). For the PSO model, data from the CIMPASI-1, CIMPASI-2, and CIMPACT clinical trials were used. For PSO, the number of observed SIEs was insufficient for robust statistical analyses to be conducted, so time-varying risk was estimated for all SAEs.

Time-varying covariates included disease activity, age, systemic CS use, and log CZP plasma concentration. These variables were measured at baseline and were reassessed and updated at every visit immediately before each CZP administration, approximately every 2 weeks. Each model was adjusted for the following baseline covariates: sex, disease duration, MTX use (RA model only), BMI, and the presence of one or more comorbidities. For the latter, patient medical history and/or medication use data (identified by review of medical records at baseline) from the five studies in the time-varying models were used. Patients were considered to have a comorbidity if they had one or more of the following: diabetes mellitus, COPD/asthma, hyperlipidemia, osteoporosis, or depression, in keeping with the age-adjusted comorbidity index previously developed (33).

Disease activity and disability measurements. The Disease Activity Score 28 joint assessment with C-Reactive Protein (DAS28-CRP) and the Simplified Disease Activity Index (SDAI) were used as measures of disease activity in patients with RA. Categories included remission (REM) or low disease activity (LDA) (DAS28-CRP < 2.7) and moderate disease activity (MDA) or high disease activity (HDA) (DAS28-CRP ≥ 2.7) (34,35). Disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI).

For PSO, time-varying disease activity was assessed using the absolute Psoriasis Area and Severity Index (PASI) and the Physician's Global Assessment (PGA) score (36). Moderate to severe disease activity with a PASI of 12 or more and PGA score of 3 or more was required for enrollment onto CIMPASI-1/-2 and CIMPACT.

Disease activity prior to AEs of potential concern. Patients with RA were categorized as having REM/LDA or MDA/HDA according to the last recorded DAS28-CRP measurement prior to study withdrawal due to MACE or cardiac death to explore potential associations with disease activity level.

Cholesterol levels and risk of MACEs. To explore potential associations between patient cholesterol level and risk of MACEs, patients with MACEs were categorized by cholesterol level at baseline and at the last measurement prior to the event. Data were available from seven studies across indications (two in RA, one in axSpA, one in PsA, and three in PSO). Total cholesterol levels were classified as low (<200 mg/dl), moderate (200-239 mg/dl), or high (>239 mg/dl) (37).

Population attributable fraction. The proportion of SIEs and MACEs in the total population attributable to either obesity (BMI ≥30 kg/m^2) or systemic CS use were calculated as population attributable fractions as follows: $PAF = \frac{O - E}{O}$, in which O refers to the observed number of cases and E is the expected

number of cases in the control group (BMI 18 kg/m^2 to <25 kg/m^2 or no systemic CS use).

RESULTS

Baseline patient characteristics. In total, 8747 CZP-treated patients were included in the study, including 6927 patients with RA, 1112 with PSO, 393 with PsA, and 315 with axSpA. Total CZP exposure varied across indications but was greatest for RA (13 542 PY) and PSO (1481 PY; Table 1). Patient baseline demographics and treatment characteristics are presented in Table 1.

Observed incidence of SAEs across indications. IRs of SAEs for each CZP indication have been reported previously (summarized in Supplemental Table S1) (24). SIEs were most common, with an overall IR of 3.03/100 PY (95% CI: 2.78-3.31). Overall IRs for MACEs and malignancies were 0.56/100 PY (95% CI: 0.45-0.68) and 0.85/100 PY (95% CI: 0.71-1.00), respectively; for malignancies excluding NMSCs, the overall IR was 0.70/100 PY (95% CI: 0.58-0.84).

Baseline predictors of SAE risk across indications. *Cox proportional hazards model of time to first SIE.* A BMI of 35 kg/m^2 or greater was associated with an increased SIE risk (HR = 1.44 [95% CI: 1.10-1.88]) relative to the normal BMI range (18.5 kg/m^2 to <25 kg/m^2); no other BMI category showed an association with SIE risk (Figure 1A). Systemic CS use also increased SIE risk (HR = 1.40 [95% CI: 1.40-1.68]). Across all indications, 16.6% of SIEs were attributable to systemic CS use at baseline. Baseline risk of SIEs was lower in PsA and PSO compared with RA (HR = 0.59 [95% CI: 0.38-0.92] and 0.44 [95% CI: 0.28-0.70], respectively). Baseline SIE risk was also lower in axSpA (HR 0.67 [95% CI: 0.39-1.09]), although this difference was not statistically significant. Compared with patients aged less than 45 years old, twice as many patients aged 65 years old or older experienced an SIE (HR = 2.19 [95% CI: 1.66-2.88]); there was no significant difference in risk between the 45 years to 65 years or younger and less than 45 years age groups. Disease duration of 10 or more years (compared with <1 year) was associated with an increased risk of SIEs (HR = 1.39 [95% CI: 1.05–1.84]). Baseline MTX use and sex were not associated with SIE risk in this model.

Cox proportional hazards model of time to first malignancy. Older age was associated with a greater risk of any malignancy (including NMSCs); HR values of 6.28 (3.05-12.95) and 16.37 (7.75-34.57) for ages of 45 years to less than 65 years and 65 or more years, respectively, when compared with an age of less than 45 years (Figure 1B). Disease duration was inversely associated with the risk of malignancy; patients diagnosed 10 or more years prior had a lower risk than those diagnosed less than 1 year prior (HR = 0.56 [95% CI: 0.35-0.92]). Prior anti-TNF treatment had no significant impact on the risk of malignancy. No other factors (indication, gender, BMI) were included in the model as no association with malignancy risk was observed ($P > 0.25$).

Cox proportional hazards model of time to first MACE. The Cox model for time to first MACE (Figure 1C) identified BMI of 35 kg/m^2 or more as a risk factor (HR = 2.07 [95% CI: 1.12–3.18] when compared with the normal BMI range). A BMI of 30 kg/m^2

Table 1. Population baseline characteristics for CZP-treated patients

	Overall (N = 8747; 17 317 PY)	RA (n = 6927; 13 542 PY)	axSpA (n = 315; 978 PY)	PsA (n = 393; 1316 PY)	PSO (n = 1112; 1481 PY)
Mean age, years (SD)	51.3 (12.7)	53.0 (12.2)	39.8 (11.9)	47.7 (11.3)	45.4 (13.0)
Age category, n (%)					
≥18 yr to <45 yr	2495 (28.5)	1609 (23.2)	203 (64.4)	154 (39.2)	529 (47.6)
≥45 yr to <65 yr	4954 (56.6)	4131 (59.6)	104 (33.0)	214 (54.5)	505 (45.4)
≥65 yr	1298 (14.8)	1187 (17.1)	8 (2.5)	25 (6.4)	78 (7.0)
Female sex, n (%)	6201 (70.9)	5491 (79.3)	119 (37.8)	218 (55.5)	373 (33.5)
BMI, mean (SD), kg/m^2	28.2 (6.7)	27.8 (6.6)	27.6 (5.9)	29.8 (6.5)	30.1 (6.9)
BMI class, n (%)					
<18.5 kg/m^2	219 (2.5)	196 (2.8)	7 (2.2)	4 (1.0)	12 (1.1)
≥18.5 kg/m^2 to <25 kg/m^2	2881 (32.9)	2465 (35.6)	105 (33.3)	86 (21.9)	225 (20.2)
≥25 kg/m^2 to <30 kg/m^2	2806 (32.1)	2149 (31.0)	105 (33.3)	144 (36.6)	408 (36.7)
≥30 kg/m^2 to <35 kg/m^2	1578 (18.0)	1180 (17.0)	57 (18.1)	88 (22.4)	253 (22.8)
≥35 kg/m^2	1236 (14.1)	916 (13.2)	36 (11.4)	70 (17.8)	214 (19.2)
Disease duration, mean (SD), yr	8.0 (8.8)	6.4 (6.9)	6.8 (7.5)	8.6 (8.3)	18.4 (12.3)
Disease duration class, n (%)					
<1 yr	1730 (19.8)	1591 (23.0)	80 (25.4)	39 (9.9)	20 (1.8)
≥1 yr to <5 yr	2529 (28.9)	2161 (31.2)	92 (29.2)	135 (34.4)	141 (12.7)
≥5 yr to <10 yr	1913 (21.9)	1585 (22.9)	61 (19.4)	90 (22.9)	177 (15.9)
≥10 yr	2575 (29.4)	1590 (23.0)	82 (26.0)	129 (32.8)	774 (69.6)
Systemic CS use, n (%)	3496 (40.0)	3200 (46.2)	160 (50.8)	99 (25.2)	37 (3.3)
MTX use, n (%)	5741 (65.6)	5435 (78.5)	55 (17.5)	250 (63.6)	1 (0.1)
Prior anti-TNF drug use, n (%)	1555 (17.8)	1283 (18.5)	49 (15.6)	75 (19.1)	148 (13.3)

Abbreviation: axSpA, axial spondyloarthritis; BMI, body mass index; CS, corticosteroid; CZP, certolizumab pegol; MTX, methotrexate; PsA, psoriatic arthritis; PSO, psoriasis; PY, patient-years; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

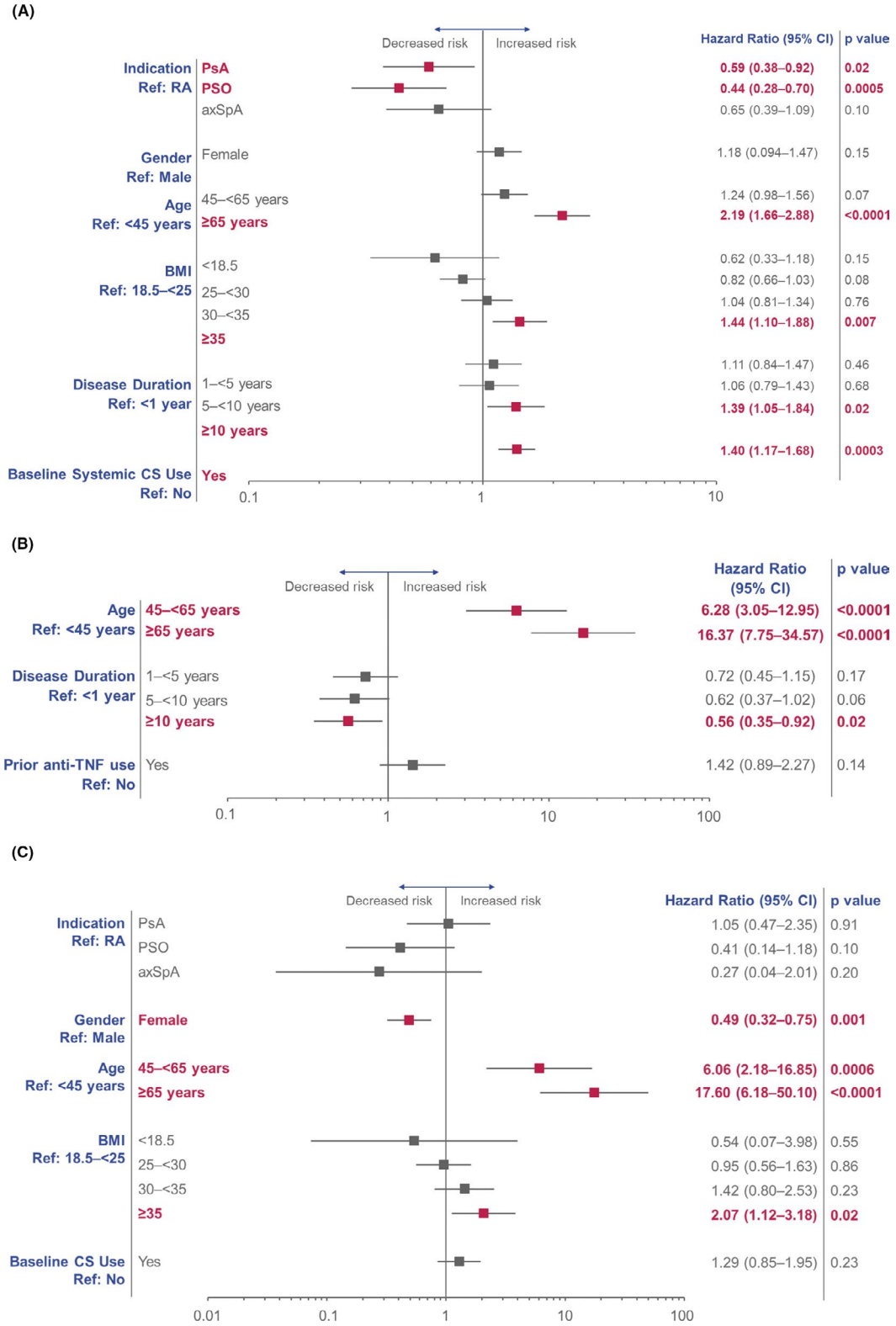

Figure 1. Cox proportional hazard models of time to first serious adverse event. **A**, Serious infectious events. **B**, Malignancies. **C**, Major adverse cardiovascular events. The variables shown result from a stepwise selection procedure with $P < 0.25$ for entry and retention into the model. Covariates, including body mass index (BMI) and corticosteroid (CS) use, were not kept in the model if $P > 0.25$ for all categories examined. A covariate was defined as a risk factor if $P \leq 0.05$ (pink boxes). All P values are nominal and should be interpreted in an exploratory manner. axSpA, axial spondyloarthritis; CI, confidence interval; PsA, psoriatic arthritis; PSO, psoriasis; RA, rheumatoid arthritis; Ref, reference category; TNF, tumor necrosis factor. [Color figure can be viewed at wileyonlinelibrary.com]

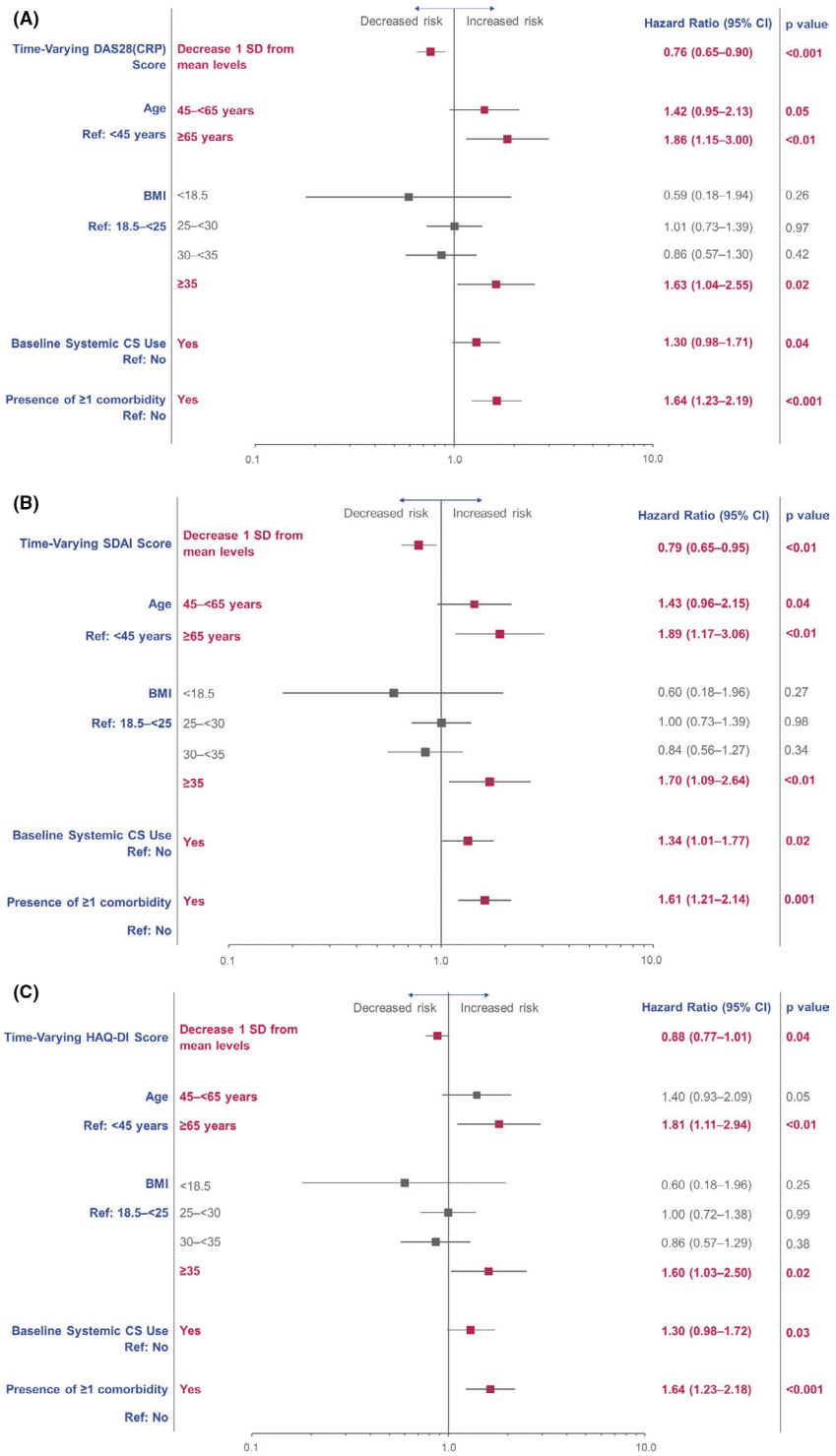

Figure 2. Cox proportional hazard models of time-varying risk of SIEs in rheumatoid arthritis (RA). **A**, Disease Activity Score 28 -joint assessment with C-Reactive Protein [DAS28(CRP)]. **B**, Simplified Disease Activity Index (SDAI). **C**, Health Assessment Questionnaire Disability Index (HAQ-DI). The variables shown result from a stepwise selection procedure with $P < 0.25$ for entry and retention into the model. Covariates, including body mass index (BMI) and corticosteroid (CS) use, were not kept in the model if $P > 0.25$ for all categories examined. A covariate was defined as a risk factor if $P \leq 0.05$ (pink boxes). Variables are shown only when at least one category was a risk factor with $P \leq 0.05$. All P values are nominal and should be interpreted in an exploratory manner. A decrease of 1 SD from the mean for each measure of rheumatoid arthritis disease activity corresponds with actual unit values as follows: DAS28(CRP) = 1.51; SDAI = 16.34; and HAQ-DI = 0.67. Patients were considered to have a comorbidity if they had one or more of the following: diabetes mellitus, chronic obstructive pulmonary disease/asthma, hyperlipidemia, osteoporosis, or depression. CI, confidence interval; Ref, reference category. [Color figure can be viewed at wileyonlinelibrary.com]

to less than 35 kg/m^2 was also associated with an increased risk of MACEs, although this was not significant (HR = 1.42 [95% CI: 0.80-2.53]). Obesity (BMI ≥ 30 kg/m^2) (38) contributed to 13.8% of all MACEs. Female patients had a lower risk of MACEs than male patients (HR = 0.49 [95% CI: 0.32-0.75]). Compared with those less than 45 years old, the risk of MACEs increased with age (45 yr to <65 ys: HR = 6.06 [95% CI: 2.18-16.85]; ≥65 years: HR = 17.60 [95% CI: 6.18-50.10]). No significant association was found between systemic CS use, MTX use, or prior anti-TNF treatment on the risk of MACEs. Of MACE cases, 16.5% were attributed to baseline systemic CS use. As previously reported (24), there were a total of 43 VTEs in the 17 317 PY included in this analysis. Across indications, a smaller proportion of patients with MACEs had high cholesterol levels at the time of the event; 12% (3/25) of patients recorded high (>239 mg/dl) cholesterol levels; the remainder of MACEs were divided equally between the low (<200 mg/dl) and moderate (200–<239 mg/dl) cholesterol groups, with 44% (11/25) in each. Of the 81 patients with RA who had MACEs, 28 (34.6%) had REM/LDA, whereas 53 (65.4%) had MDA/HDA. Of the 17 cardiac deaths recorded, four (23.5%) and 13 (76.5%) were in the REM/LDA and MDA/HDA groups, respectively.

Time-varying risk factors for SIEs in RA. In the Cox model examining the impact of time-varying factors on SIE risk in patients with RA, an improvement (reduction in disease activity) of 1 SD in DAS28-CRP (1.51 units) relative to the mean baseline score was associated with a decrease in SIE risk (HR 0.76 [95% CI: 0.65-0.90]; Figure 2A). When patient time was categorized by DAS28-CRP score, the overall incidence of SIEs was lowest during time spent in remission (IR = 3.1/100 PY [95% CI: 2.2-4.2]), whereas periods of HDA were associated with the highest SIE incidence (IR = 5.9/100 PY [95% CI: 4.6-7.3]; Table 2). Age of 65 years or older at any time throughout the studies was the strongest predictor of SIE risk, with an HR of 1.86 (95% CI: 1.15-3.00) when compared with patients aged less than 45 years. Time-varying systemic CS use was also a predictor of SIE risk (HR = 1.30 [95% CI: 0.98-1.71]). Baseline factors contributing to SIE risk in the time-varying model included BMI of 35 kg/m^2 or more (HR = 1.63 [95% CI: 1.04-2.55] compared with normal BMI range) and the presence of one or more comorbidities (HR = 1.64 [95% CI: 1.23-2.19] compared with no comorbidities).

When DAS28-CRP was replaced with SDAI as a time-varying measure of disease activity (Figure 2B), an improvement of 1 SD (16.34 units) relative to the mean was associated with an HR of 0.76 (95% CI: 0.65-0.95). Consistent with the findings of the DAS28-CRP model, age of 65 years or more, time-varying systemic CS use, baseline BMI of 35 kg/m^2 or more, and one or more comorbidities at baseline were identified as predictors of SIE risk. An improvement of 1 SD in HAQ-DI (0.67 units) over time (Figure 2C) was also associated with a decreased risk of SIEs (HR = 0.88 [95% CI: 0.77-1.01]). The same factors predicting SIE risk in the DAS28-CRP model were shown to increase SIE risk in the HAQ-DI model; estimated effects were similar to those found for the DAS28-CRP.

Across the three Cox models for time-varying risk factors for SIEs in RA, time-varying plasma CZP concentration, sex, baseline MTX use, and baseline disease duration were not significantly associated with the risk of SIEs.

Time-varying risk factors for SAEs in PSO. In the Cox model examining PASI as a time-varying covariate in PSO (Figure 3A), an improvement of 1 SD (7.46 units) from the mean PASI did not significantly decrease the risk of SAEs (HR = 1.09 [95% CI: 0.81-1.46]). Age was a significant predictor of increased SAE risk in PSO (45 to <65 yr: HR = 1.67 [95% CI: 1.14-2.44] and ≥65 years: HR = 2.37 [95% CI: 1.32-4.26] compared with <45 years). However, the most prominent risk factor for SAEs in PSO was time-varying systemic CS use, with an HR of 3.01 (95% CI: 1.06-8.85). These results were mirrored in the Cox model examining PGA as a time-varying covariate (Figure 3B); an improvement of 1 SD (1.13 units) from the mean PGA score did not significantly decrease the risk of SAEs (HR = 1.22 [95% CI: 0.90-1.40]). Older age was associated with significantly increased risk (45 to <65 years: HR = 1.68 [95% CI: 1.15-2.45] and ≥65 years: HR = 2.39 [95% CI: 1.33-4.31]), and systemic CS use was associated with more than three times elevated risk of SAEs compared with no systemic CS use (HR = 3.16 [95% CI: 1.09-9.12]).

DISCUSSION

Although anti-TNF medications are effective treatments for IMIDs, clinical and demographic factors may confer different

Table 2. Observed incidence of SIEs in RA by DAS28-CRP disease activity category (n = 1601)

	HDA (>4.1)	MDA (>2.7 to ≤4.1)	LDA (≥2.3 to ≤2.7)	Remission (<2.3)
Patient time,a PY	1465	1318	889	784
Number of SIEs	85	79	24	42
IR/100 PY (95% CI)	5.9 (4.6-7.3)	3.3 (2.6-4.1)	3.5 (2.2-5.2)	3.1 (2.2-4.2)

Abbreviation: CI, confidence interval; CZP, certolizumab pegol; DAS28-CRP, Disease Activity Score 28-joint assessment with C-reactive protein; HDA, high disease activity; IR, incidence rate; LDA, low disease activity; MDA, moderate disease activity; PY, patient-years; RA, rheumatoid arthritis; SIE, serious infectious event.
[a] Patient time was grouped according to the lowest disease activity assessment recorded per 12-week period over the course of CZP exposure; patients can be included in more than one disease activity category.

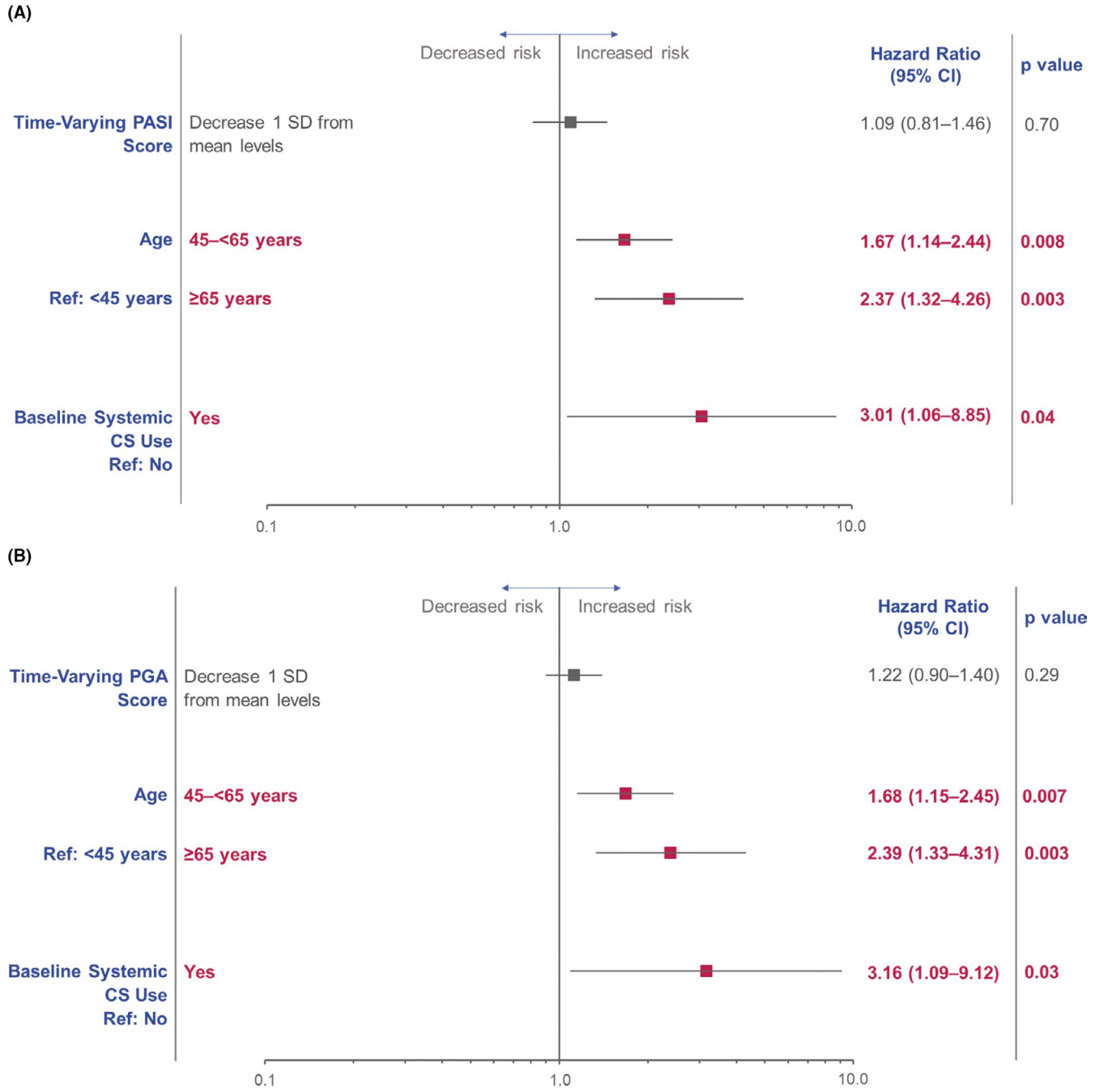

Figure 3. Cox proportional hazard models of time-varying risk of serious adverse events in psoriasis (PSO). **A**, PSO Area and Severity Index (PASI). **B**, Physician's Global Assessment (PGA). The variables shown result from a stepwise selection procedure with $P < 0.25$ for entry and retention into the model. Covariates, including body mass index (BMI) and corticosteroid (CS) use, were not kept in the model if $P > 0.25$ for all categories examined except for time-varying PASIs and PGA, which were forced into the model. A covariate was defined as a risk factor if $P \leq 0.05$ (pink boxes). Variables were shown only when at least one category was a risk factor with $P \leq 0.05$ except for time-varying PASIs and PGA. A decrease of 1 SD from the mean for each measure of PSO disease activity corresponds with actual unit values as follows: PASI = 7.46 and PGA = 1.13. All *P* values are nominal and should be interpreted in an exploratory manner. Ref, reference category. [Color figure can be viewed at wileyonlinelibrary.com]

levels of risk of SAEs among patients and potentially influence treatment response. Using safety data pooled across 34 CZP clinical trials, this study investigated the contribution of specific patient characteristics to the risk of different SAEs in CZP-treated patients across indications. The most frequently reported SAE across indications was SIEs, in line with previous safety reports of anti-TNF agents (24,39,40). These results suggest that age of 65 years or more is a significant risk factor for SIEs, malignancies, and MACEs. For SIEs specifically, age of 65 years or more, BMI of 35 kg/m^2 or more, and systemic CS use were associated with

increased AE risk based on baseline data pooled across indications, as well as over time within the RAPID1/RAPID2 RA population. In this study, CZP concentration in plasma did not contribute to SIE risk. In the models including time-varying covariates in RA, decreases in disease activity (based on DAS28-CRP or SDAI assessment tools) and disability (HAQ-DI score) were also estimated to significantly reduce SIE risk. Disease activity did not contribute significantly to the time-varying risk of SAEs in PSO; however, systemic CS use and age were identified as significant predictors of SAE risk.

Disease duration was inversely associated with the risk of malignancy. Although this result may seem counterintuitive given the increased risk of malignancy with age, it has been previously reported that the incidence of malignancies is higher for several years following RA diagnosis, and this decreases over time (41). Possible explanations for a reduced risk of malignancy with greater disease duration include long-term drug positive effects with lower disease activity or early mortality among patients with severe disease activity or comorbidities. Additionally, it may be that malignancy is identified earlier in patients with a recent diagnosis of RA, as, together with their health care practitioners, they may be more acutely aware of changes in their physical health and symptoms. It is likely that a number of factors contribute to this observation (42). The risk of malignancy was more than 16 times higher for patients aged 65 years or older compared with those aged less than 45 years; this risk, although substantial, is comparable with the general population (41,43). Our current study suggests that the risk of malignancies is not disproportionally increased by the presence of IMIDs or anti-TNF treatment.

Despite a higher average BMI among patients with PSO, the IR of MACEs was higher in patients with RA (0.62/100 PY versus 0.27/100 PY). These results support previous evidence that RA may be an independent cardiovascular risk factor, possibly because of the loss of muscle mass and increased fat mass (with potentially normal BMI) associated with rheumatoid cachexia (44,45). Higher CS use in patients with RA in this study population may also have contributed to the higher IR of MACEs in this population compared with the PSO population. The finding that most patients who experienced MACEs had low cholesterol levels at baseline and prior to the event seems contrary to expectations but may be explained by the "lipid paradox," in which there is a paradoxical association between lower total cholesterol and low-density lipoprotein levels and the risk of cardiovascular disease in patients with RA (46). A further consideration for this finding is that low cholesterol may have resulted from statin use in patients who had previously had MACEs or who were already at higher risk of MACEs because of factors such as family history and hypertension. Statin use could not be accounted for in this analysis, as this was not recorded in the trials included. This finding should therefore be interpreted with caution.

Patients met the eligibility criteria for inclusion in the clinical trials included in this analysis, and so they may not be truly representative of the real-world population of individuals with IMIDs. However, although more than 70% of patients were female and the mean age in the trials was generally older than 40 years, this is broadly consistent with findings reported in epidemiological studies (47,48).

Grouping all SAEs in the Cox model including time-varying covariates for PSO is an important limitation of the study because the event types analyzed are different in nature and may have been influenced by different risk factors. It was not possible to include comorbidities in the cross-indication Cox models including the baseline characteristics, as the data were not included in the original pooled analyses. However, previous findings from Cox proportional hazards modeling of SIE risk in CZP-treated patients with RA suggest that age-adjusted baseline comorbidities are a strong predictor of SIE risk (33). It is likely that there are associations between comorbidities and other analyzed risk factors. For example, increased SIE risk in patients with obesity could be attributed to comorbidities such as diabetes and COPD (49,50). Similarly, the higher risk of SAEs in patients aged 65 years or more could be due to the increased probability of developing more comorbidities with age (51). There is also the possibility that patients with multimorbidity may be less likely to attain LDA or REM and consequently more likely to contract infections. Therefore, although patient characteristics are of clinical importance, assigning causality is complex given the multifactorial nature of SAEs in IMIDs.

This long-term, cross-indication, pooled analysis of clinical trial data representing more than 17 000 PY of CZP exposure examined the impact of patient characteristics, including time-varying disease activity, and comedication on the risk of AEs. Overall, the long-term safety profile of CZP was consistent with previous findings. Age, high BMI, and systemic CS use were predictors of SIEs across indications (33). Risk of malignancies was greater in older patients, whereas obesity and male sex were predictors of MACE risk, in line with the general population. Modeling including time-varying covariates demonstrated that a reduction in RA disease activity significantly reduced the risk of SIEs, suggesting that good disease management may lead to fewer AEs. These results suggest that clinicians should take patient characteristics and disease activity into account when making treatment decisions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Nicola Tilt and Christina Popova had full access to all

of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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