

Cigarette smoking and clinical response to certolizumab pegol treatment in Hungarian, Czech, and Slovak patients with rheumatoid arthritis: 104-week data from the CIMDORA prospective, non-interventional study

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Abstract

Objective

Smoking has been shown to influence rheumatoid arthritis (RA) severity and reduce response to some anti-tumour necrosis factor (anti-TNF) therapies. CIMDORA assessed the association between cigarette smoking and clinical effectiveness of certolizumab pegol (CZP) in Hungarian, Slovak, and Czech RA patients.

Methods

CIMDORA was a prospective, non-interventional, 104-week study (Feb 2011–Aug 2015). The primary endpoint was association between change in 28-joint Disease Activity Score (DAS28[ESR]) from baseline to Week 12, and baseline cigarette pack-year history. Secondary endpoints included association between change in DAS28(ESR) and daily number of cigarettes smoked. The full analysis set (FAS) included all patients receiving ≥ 1 dose of CZP with all necessary assessments for the primary endpoint. Treatment-emergent adverse events (TEAEs) were reported for all patients receiving ≥ 1 dose of CZP.

Results

The FAS included 218/273 enrolled patients: 155 Hungarian, 46 Czech and 17 Slovak. Hungarian and Czech patients completed 104 weeks ($n=141$); Slovak patients completed 52 weeks. Mean change in DAS28(ESR) [SD] at Week 12 (-2.78 [1.47]) was not significantly associated with baseline cigarette pack-year history (slope estimate [SE]: 0.03, 95% confidence interval [CI]: -0.16, 0.21 [$p=0.77$]). Mean DAS28(ESR) [SD] reductions to Week 52 (-3.33 [1.33]) were not significantly associated with daily number of cigarettes smoked in the previous month (SE: 0.001, CI: -0.05, 0.05 [$p=0.95$]). Two deaths were reported but neither of them was related to CZP. No new safety signals were identified and the safety profile was consistent with previous CZP studies.

Conclusion

After 104 weeks of CZP treatment, patients demonstrated similar DAS28(ESR) improvements, irrespective of smoking history.

Key words

rheumatoid arthritis, cigarette smoking, anti-rheumatic agents, tumour necrosis factor-alpha

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic autoimmune disease, characterised by swollen and tender joints, and the destruction of synovial joints (1, 2). RA is associated with a high prevalence of comorbidities and most patients require disease-modifying anti-rheumatic drug (DMARD) treatment to delay or stop disease progression (3-5).

The environmental risk factors affecting the course and outcome of RA include smoking, infections, dietary intake, stress, geographical location, socio-economic status and birthweight (6, 7). Smoking is associated with an increased risk for RA and higher disease burden in patients with RA (8-12), and has been suggested as a predictor for anti-tumour necrosis factor (TNF) discontinuation in patients with RA (13). Smokers are known to have elevated TNF- α levels and TNF is thought to contribute to chronic obstructive pulmonary disease (COPD) (14). Anti-TNF therapies have, however, not been effective in COPD, but at the same time, this treatment did not produce any deleterious effect on COPD or the number of its exacerbations (15, 16). Despite mixed reports on the effect of smoking on the effect of biologics (17), the most robust studies demonstrated an overall reduction in response to anti-TNF therapies (infliximab, etanercept, adalimumab) in current RA patients who smoke (18-20).

Certolizumab pegol (CZP) is a PEGylated, Fc-free anti-TNF (21, 22) approved for the treatment of moderate to severe RA, in adult patients, after inadequate response to conventional DMARDs, including methotrexate. CZP treatment has demonstrated improved clinical, radiographic and patient reported outcomes in RA patients with varying disease severity, irrespective of concomitant or prior treatments used (23-27). No differences in patients' clinical response to CZP were observed among patients with RA, who were active smokers and were enrolled in the RENACER registry in Spain (28). In this real world evidence study, we evaluated the association of smoking status at baseline, and cigarette consumption,

on the clinical response to CZP in patients with RA from Hungary, Slovakia, and the Czech Republic.

Methods

Patients

Eligible patients were ≥ 18 years old, male or female, and were receiving CZP treatment for RA, according to the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) and country specific guidelines. Patients were enrolled from Hungary, the Czech Republic and Slovakia after the provision of informed consent. The physicians' decision to prescribe CZP was made prior to the patients' inclusion in the study. Patients enrolled into the study included both smokers and non-smokers.

Patients were deemed ineligible if they met any of the contraindications of CZP treatment, had a known hypersensitivity to any of the components of CZP, or had previously been treated with CZP. Patients confirmed pregnant were excluded. Time to discontinuation of CZP from the baseline visit was reported.

Ethics approval and consent to participate

Ethical approval was provided by the Hungarian Ethics Committee (ETT-TUKEB) with REC approval number 17277-0/2010-1018 EKU (724/PI/10). The extension of the study to Week 104 was approved by the same ethics committee (REC approval number: 44728/2012 EKU). Submission of non-interventional studies to the ethics committees in the Czech Republic and Slovakia was not required at the time of the study initiation. All patients included within the CIMDORA study provided written, informed consent, prior to recruitment onto the study.

Study design

CIMDORA was a non-interventional, prospective, non-comparative, post-marketing study. The study duration was extended to 104 weeks in Hungary, and the Czech Republic, but the extension was not applied in Slovakia, where patients completed the study at Week 52. CZP administration was according to usual clinical practice (SmPC)

and consisted of a loading dose of 400 mg at Weeks 0, 2, and 4, followed by a maintenance dose of 200 mg every two weeks (Q2W); CZP was provided to patients on prescription from the treating physician.

Study procedures and evaluations

A self-reported smoking habits questionnaire was completed at baseline and used to determine cigarette smoking history (Supplementary Fig. 1). The questionnaire assessed whether patients had previously, or currently smoked tobacco, and how many cigarettes they smoked per day, the type of tobacco product used (*e.g.* cigarette, pipe, cigar), whether patients had ever tried to stop smoking, and if so, for how long. Smoking history was defined using pack-year history, which was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years that the patient had smoked as follows (29):

$$\text{Pack-year history} = \left(\frac{\# \text{cigarettes per day}}{20} \right) * \text{smoking years}$$

One pack of cigarettes was defined as 20 cigarettes to convert to packs per day. If patients reported a break in smoking of ≥ 1 year in duration, this time period was subtracted from the years of smoking. For patients who reported smoking tobacco in forms other than cigarettes, the following conversion factors were used: 1 cigar=4 cigarettes, 1 pipe=2.5 cigarettes and 1 cigarillo=2 cigarettes. Patients who recorded their smoking status as having 'never smoked' were classified as having a cigarette pack-history of 0; this included patients who smoked < 1 pack of cigarettes (*i.e.* < 20 cigarettes) in a year.

Patients' current smoking status was recorded, and cigarette consumption was assessed by measuring the number of cigarettes smoked per day during the previous month at Weeks 12, 24, 52, and 104.

The primary endpoint was the association between change in 28-joint Disease Activity Score Erythrocyte Sedimentation Rate (DAS28[ESR]) from baseline to Week 12 and the cigarette pack-year history recorded at baseline. Secondary endpoints included the association

of cigarette pack-year history, or the number of cigarettes smoked per day during the previous month, with change of DAS28(ESR) from baseline to Week 24, 52, and 104, and the association between cigarette pack-year history and change in C-reactive protein (CRP) level from baseline to Week 52. The association of anti-cyclic citrullinated peptide (anti-CCP), and/or rheumatoid factor (RF) with cigarette pack-year history were also assessed at baseline, for patients with these data available.

Clinical data

CRP and ESR levels, swollen joint count (SJC), tender joint count (TJC), and Patients' Global Assessment of Disease Activity (PtGADA), using visual analogue scales (VAS; in cm), were recorded for all patients at Weeks 0, 4, 8, 12, 24, 36, and 52, as well as at Week 104 in Hungary and the Czech Republic. Additionally, RF, anti-CCP and antinuclear antibody levels were measured at baseline per routine clinical practice, although this assessment was optional for patients enrolled in the study.

Safety measurements

Safety assessments were mainly based on treatment emergent adverse events (TEAEs), defined as any adverse event (AE) on, or after, the first dose of CZP injection, and up to 70 days after the last CZP injection. Incidence of all TEAEs and pregnancies were documented by the treating physician, and TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1, and were reported by severity (mild, moderate, severe). Additional details on injection site reactions were also collected at each visit.

Statistical analysis

Descriptive statistics were used for continuous variables and are reported as mean, standard deviation (SD), median and interquartile range. For categorical variables, absolute counts (n) and percentages are reported. Missing data were not imputed, and only observed data are presented. In order to detect significant associations between change in DAS28(ESR) from baseline to Week

12, a sample size of 120 patients was required to achieve at least 90% power; this was subsequently increased to recruit more patients with a smoking history.

The Safety Set included all patients who received at least one dose of CZP at any point up to Week 104 during the study. The full analysis set (FAS) included all enrolled patients, who received ≥ 1 dose of CZP and provided at least data on pack-year history at baseline and DAS28(ESR) at baseline and Weeks 4, 8 or 12.

Correlation between smoking and clinical response to CZP was assessed by the association of change from baseline in DAS28(ESR) at Week 12 with cigarette pack-year history. This correlation was analysed using a *t*-test of the regression parameter, after performing a simple linear regression. The linear regression included DAS28(ESR) as the dependent variable, and the intercept and the pack-year history were used as the continuous, independent variables; this was carried out using a multiple regression model to reduce the risk of bias. Results with *p* values ≤ 0.05 were considered to be significant. Additionally, the correlation between change in DAS28(ESR) and the number of cigarettes smoked per day in the previous month, measured at Weeks 12, 24, 52 and 104 of CZP treatment, was assessed using Spearman correlation coefficients, and by calculation of the simple linear regression analogue to the primary analysis. Correlation between change in DAS28(ESR) at Weeks 24 and 52 of CZP treatment and the number of pack-years at baseline was measured in the same way as the primary variable.

The correlation of change in CRP level from baseline to Week 52 of CZP treatment and cigarette pack-year history at baseline was determined using Spearman correlation coefficients. The association between baseline anti-CCP or RF level with baseline cigarette pack-year history was measured using a linear model.

Results

Patient disposition and baseline characteristics

Overall, 273 patients were enrolled in the study between February 2011 and

August 2015, including 197 from Hungary, 55 from the Czech Republic, and 21 from Slovakia; all patients received CZP treatment. A total of 218 patients were analysed within the FAS (155 from Hungary, 46 from the Czech Republic, and 17 from Slovakia). The reasons for exclusion from the FAS included missing pack-year history at baseline (n=9), DAS28(ESR) score missing at baseline, Week 4, 8 or 12 (n=40), treatment with CZP before starting the study (n=6), and initiation of CZP >14 days prior to baseline (n=1); one patient had 2 protocol deviations. A total of 141/218 patients (64.7%) from Hungary and the Czech Republic completed 104 weeks of CZP treatment. Within the FAS, 116/218 (53.2%) patients remained on CZP treatment after the last study visit at Week 104. Patients from Slovakia were not analysed separately, due to the small number of enrolled patients.

The mean age (SD) of patients was 53.1 (11.6) years, and the majority (86.7%) of patients were female (Table I). A total of 123/218 (56.4%) of patients reported in the baseline smoking questionnaire that they had never smoked; of those who had ever smoked, 55/95 (57.9%) reported that they were current smokers (Fig. 1). More than half (60.6%) of the patients had a cigarette pack-history <1, which included non-smokers (Table I); mean (SD) number of cigarettes smoked by previous smokers was 10.4 (7.8) cigarettes/day. In Hungary and the Czech Republic, 77 (49.7%) and 31 (67.4%) patients, respectively, were non-smokers.

Association between smoking and DAS28(ESR) response to CZP at Week 12

The mean (SD) change from baseline in DAS28(ESR) after 12 weeks of CZP treatment was -2.78 (1.47) (Table II). In CZP-treated patients, the change from baseline in DAS28(ESR) at Week 12 was not significantly associated with cigarette pack-year history at baseline (slope estimate=0.03, 95% confidence interval [CI] -0.16, 0.21, [p=0.77]); similar results were observed for change in DAS28(CRP). Based on the Spearman's correlation coefficient (0.07), there was almost

Table I. Baseline patient demographics, disease characteristics, and smoking habits.

| | Full analysis set (FAS) (n=218), unless otherwise stated |
|--|--|
| <i>Demographics</i> | |
| Age (years), mean (SD) | 53.1 (11.6) |
| Female gender, n (%) | 189 (86.7) |
| <i>Disease characteristics</i> | |
| DAS28(ESR), mean (SD) | 6.1 (0.9) |
| Time since RA diagnosis (years), median (Q1, Q3) | 7.0 (3.0, 15.0) |
| Swollen Joint Count, mean (SD) ^a [n=273] | 9.1 (5.5) |
| Tender Joint Count, mean (SD) ^a [n=273] | 13.2 (6.5) |
| Patient's assessment of pain VAS (cm), mean (SD) ^a [n=273] | 7.0 (1.7) |
| PtGADA VAS (cm), mean (SD) ^a [n=273] | 6.9 (1.8) |
| Rheumatoid factor (U/mL) ^b , median (Q1, Q3) [n=129] | 61.9 (16.6, 138.0) |
| Positive (≥14 IU/mL), n (%) | 114 (52.3) |
| Anti-CCP (U/mL) ^c , median (Q1, Q3) [n=117] | 193.0 (17.5, 592.0) |
| Positive (≥7 IU/mL), n (%) | 90 (41.3) |
| CRP (mg/L), median (Q1, Q3) ^a [n=273] | 11.3 (5.1, 27.4) |
| ESR (mm/h), median (Q1, Q3) ^a [n=273] | 30.0 (18.0, 45.0) |
| <i>Patient-reported smoking status at baseline</i> | |
| Never smoked, n (%) | 123 (56.4) |
| Tried smoking, n (%) | 95 (43.6) |
| Current smokers, n (%) | 55 (57.9) |
| <i>Number of cigarettes smoked in previous month (cigarette/day)</i> | |
| Median (Q1, Q3) | 0.0 (0.0, 0.0) |
| Mean (SD) | 3.4 (10.6) |
| <i>Number of cigarettes smoked by previous smokers (cigarette/day)^d</i> | |
| Median (Q1, Q3) | 10.0 (3.0, 20.0) |
| Mean (SD) | 10.4 (7.8) |
| <i>Pack-year history^e</i> | |
| Median (Q1, Q3) | 0.0 (0.0, 7.5) |
| Mean (SD) | 6.5 (11.5) |
| <i>Pack-year history by category, n (%)</i> | |
| 0 | 132 (60.6) |
| 1-10 | 41 (18.8) |
| 11-20 | 17 (7.8) |
| >20 | 28 (12.8) |

^aSafety set (n=273). ^{b,c}Data are for biological treatment-naïve patients only (^bn=129, ^cn=117). ^dPatients were current non-smokers at baseline, but had smoked prior to enrolment in the study (n=38); values represent the number of cigarettes smoked while patients were smokers. ^ePack-years were calculated as either (packs smoked per day) × (years as a smoker), or ((number of cigarettes smoked per day × number of years smoked)/20). CCP: cyclic citrullinated peptide; CRP: C-reactive protein; cm: centimeters, DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate; h: hours; IU: international units; mg: milligrams; mL: millilitres; mm: millimetres; PtGADA: Patient's Global Assessment of Disease Activity; Q: quartile; SD: standard deviation; U: units; VAS: visual analogue scale.

no correlation between change from baseline in DAS28(ESR) score after 12 weeks of CZP treatment, and cigarette pack-year history at baseline, and it was not clinically relevant (p=0.31). The influence of current cigarette consumption on change in DAS28(ESR) score from baseline to Week 12 of CZP treatment remained minimal (slope estimate=0.02, 95% CI -0.02, 0.06 [p=0.27]).

Correlation between smoking and DAS28(ESR) response to CZP from baseline to Week 104

Mean improvements in DAS28(ESR)

response, from baseline until Week 104 of CZP treatment, were observed for patients in all pack-year categories (Fig. 2a). The decreases in mean DAS28(ESR) [SD] in CZP-treated patients from baseline to Week 24 (-3.13 [1.42]), Week 52 (-3.33 [1.33]), and Week 104 (-3.25 [1.35]), were weakly correlated with cigarette pack-year history at baseline, based on Spearman's correlation coefficients (Week 24: 0.02; Week 52: 0.03; Week 104: 0.02). None of these correlations were significantly different from a zero correlation at any timepoint assessed and were therefore not considered to

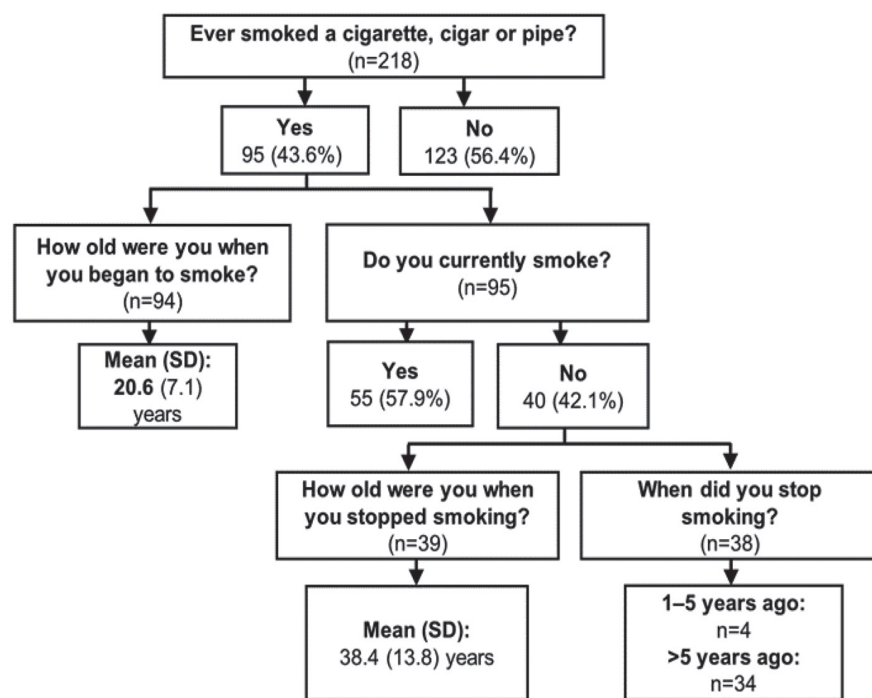


Fig. 1. Cigarette smoking at baseline. Full analysis set. Results from the smoking habits questionnaire. SD: standard deviation.

be clinically relevant (Table II). The changes in DAS28(ESR) from baseline to Weeks 12, 24, 52, and 104 were comparable between non-smokers and smokers (Fig. 2). Improvements in DAS28(ESR) response to CZP from baseline until Week 104 were observed for Hungarian (n=155), and for Czech patients (n=46) for all pack-year categories (Fig. 2b-c). The reduction in mean DAS28(ESR) between baseline and Week 24 and Week 52, respectively, were also not significantly associated with the number of cigarettes smoked per day in the pre-

vious month (Week 24: slope estimate = 0.02, 95% CI -0.03, 0.06 [p=0.47]; Week 52: slope estimate = 0.001, 95% CI -0.05, 0.05 [p=0.95]) (Table II). The slope estimates can be interpreted such that with every additional cigarette smoked per day, the DAS28(ESR) increased by 0.02 at Week 24, and 0.001 at Week 52. However, at Week 104, a weak but significant association of decrease in disease activity after CZP treatment and number of cigarettes smoked per day in the previous year was observed (slope estimate = -0.07, 95% CI -0.13, -0.01 [p<0.05]).

Correlation between smoking habits and anti-CCP or rheumatoid factor at baseline and change in CRP level from baseline to Week 52

Baseline levels of anti-CCP and RF were weakly correlated with cigarette pack-year history at baseline (Spearman's correlation coefficients: anti-CCP=0.04 and RF=0.21), but only the correlation between RF and cigarette pack-year history was significant (p<0.05) (Table III). The change in CRP level from baseline after CZP treatment for 52 weeks was weakly correlated (Spearman's correlation coefficient: 0.11) with cigarette pack-year history; this association was not significant (p=0.31).

Disease characteristics

Disease activity decreased for all parameters measured at Week 12, compared to baseline (Suppl. Table S1), and these improvements were sustained, or enhanced further, through Week 104. Patients reported a reduction in disease activity, the greatest of which was observed at Week 52.

Safety

A total of 91 TEAEs were reported by 66 (24.2%) patients (Table IV), most of which were categorised as mild to moderate. Two TEAEs were considered severe. Eighteen patients had TEAEs, which were considered to be related to the study drug; 18 (6.6%) patients reported 22 serious TEAEs. Treatment with CZP was discontinued by 16 (5.9%) patients as a result of a TEAE.

Table II. Association between CZP-induced DAS28(ESR) change from baseline with smoking.

| Week | n | DAS28(ESR) CFB, mean (SD) | Cigarette pack-year history at baseline ^a | | Current cigarette consumption ^b | |
|------|-----|---------------------------|--|---|--|---|
| | | | Spearman's correlation coefficient [p-value] | Linear regression slope estimate (95% CI) [p-value] | Spearman's correlation coefficient [p-value] | Linear regression slope estimate (95% CI) [p-value] |
| 12 | 215 | -2.78 (1.47) | 0.07 [0.31] | 0.03 (-0.16, 0.21) [0.77] | 0.10 [0.14] | 0.02 (-0.02, 0.06) [0.27] |
| 24 | 194 | -3.13 (1.42) | 0.02 [0.77] | 0.02 (-0.18, 0.21) [0.87] | 0.04 [0.64] | 0.02 (-0.03, 0.06) [0.47] |
| 52 | 169 | -3.33 (1.33) | 0.03 [0.65] | 0.001 (-0.20, 0.20) [0.99] | 0.03 [0.76] | 0.001 (-0.05, 0.05) [0.95] |
| 104 | 136 | -3.25 (1.35) | 0.02 [0.81] | 0.02 (-0.20, 0.24) [0.85] | -0.16 [0.08] | -0.07 (-0.13, -0.01) [0.03] |

Full analysis set (FAS). ^aCigarette pack-years were calculated as either (packs smoked per day) × (years as a smoker), or ((number of cigarettes smoked per day × number of years smoked)/20). ^bCurrent cigarette consumption defined as number of cigarettes smoked per day during the previous month for Weeks 12–52, and cigarettes smoked/day for the previous year for Week 104. For current cigarette consumption, n=210 at Week 12, n=177 at Week 24, n=162 at Week 52 and n=136 at Week 104 (for linear regression only). CFB: change from baseline; CI: confidence interval; CZP: certolizumab pegol; DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; SD: standard deviation.

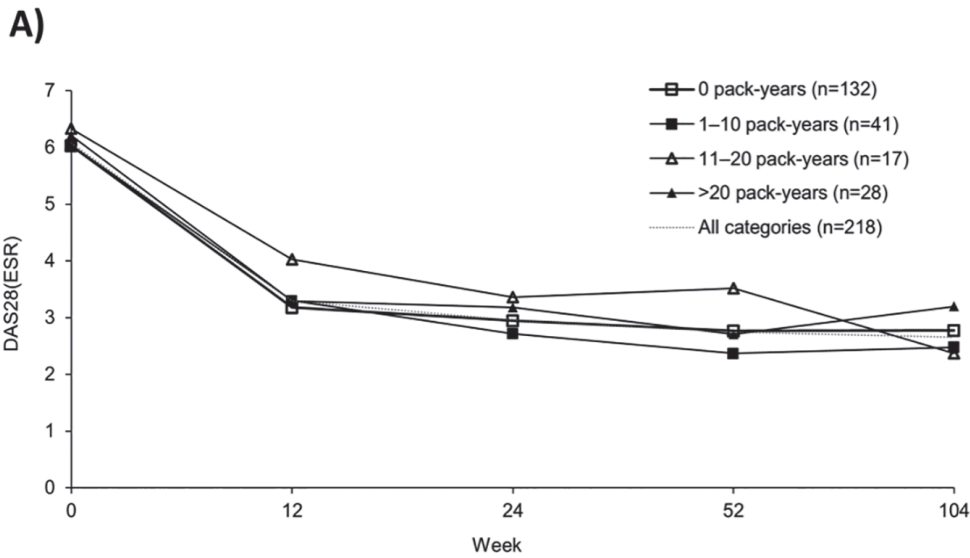


Fig. 2. Mean DAS28(ESR) by

pack-year history, for:

A: all patients

B: Hungarian patients

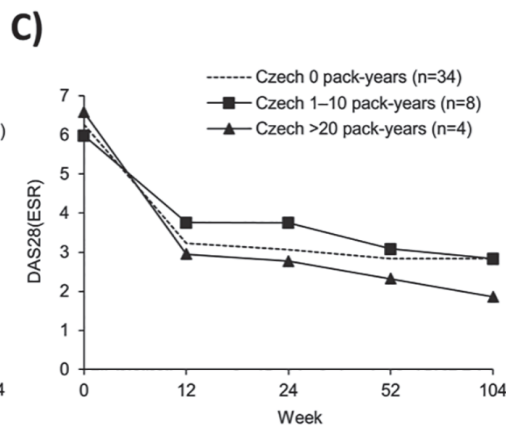
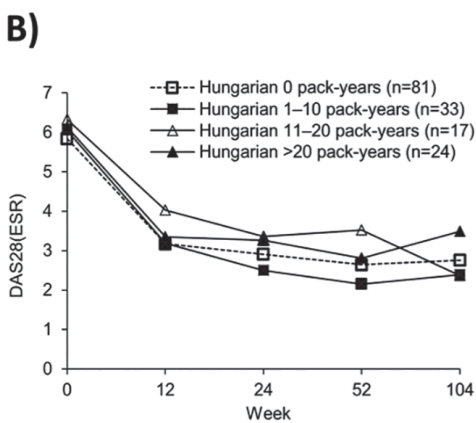
C: Czech patients

Full analysis set.

A: Data are reported from all countries until Week 52; data reported at Week 104 only includes patients from the Hungarian and Czech populations, as the Slovak cohort were only followed up until Week 52. No patients were classified within the 11–20 pack-years category in the Czech population (Fig. 1C).

DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; SD: standard deviation.

| Pack-year category | Week 0 | | Week 12 | | Week 24 | | Week 52 | | Week 104 | |
|--------------------|--------|-----------|---------|-----------|---------|-----------|---------|-----------|----------|-----------|
| | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| 0 pack-years | 132 | 6.0 (1.0) | 129 | 3.2 (1.2) | 124 | 3.0 (1.2) | 108 | 2.8 (1.2) | 84 | 2.8 (1.0) |
| 1–10 pack-years | 41 | 6.0 (1.0) | 41 | 3.3 (1.4) | 34 | 2.7 (1.3) | 29 | 2.4 (1.1) | 24 | 2.5 (1.1) |
| 11–20 pack-years | 17 | 6.3 (1.0) | 17 | 4.0 (1.5) | 12 | 3.4 (1.6) | 13 | 3.5 (1.6) | 11 | 2.4 (0.8) |
| >20 pack-years | 28 | 6.2 (0.8) | 28 | 3.3 (1.1) | 24 | 3.2 (1.4) | 19 | 2.7 (1.0) | 17 | 3.2 (1.4) |
| All categories | 218 | 6.0 (1.0) | 215 | 3.3 (1.3) | 194 | 3.0 (1.2) | 169 | 2.8 (1.2) | 136 | 2.8 (1.1) |



The most common TEAEs by system organ class (SOC) were ‘general disorders and administration site conditions’, which were described by 32 (11.7%) patients, followed by 11 (4.0%) patients reporting ‘skin and subcutaneous tissue disorders’. The most common TEAE by preferred term was ineffectiveness of the drug, which was reported by 23 (8.4%) patients. A total of 12/273 patients (4.4%) experienced 23 local reac-

tions at the site of CZP administration, but none were classified as severe. No pregnancies, nor any TEAEs related to overdose, were reported during the study. However, it should be noted that assessment of intensity and relatedness of TEAEs was not available for several patients.

Seven (2.6%) patients reported infections: two urinary tract infections (UTI), and one each of bacterial arthri-

tis, acarodermatitis, bronchitis, sepsis, tuberculosis, and viral infection. The two severe TEAEs reported (Table IV) were malignant lung neoplasm (1 patient) and non-Hodgkin’s lymphoma (1 patient), both of which were considered to be related to study drug, and CZP was therefore withdrawn from both patients.

Two deaths were reported during the study, however, neither was considered

Table III. Association between cigarette pack-year history and rheumatoid factor, anti-CCP and CRP levels.

| | n | Mean (SD) | Spearman's correlation coefficient [p-value] |
|------------------------------|-----|-----------------|--|
| Baseline RF (U/mL) | 129 | 142.65 (274.56) | 0.21 [0.02] |
| Baseline anti-CCP (U/mL) | 117 | 474.70 (737.35) | 0.04 [0.70] |
| CFB in CRP at Week 52 (mg/L) | 107 | -11.44 (26.80) | 0.11 [0.31] |

Full analysis set (FAS). Data were not available from all centres. CCP: cyclic citrullinated peptide; CFB: change from baseline; CRP: C-reactive protein; L: litre; mg: milligrams; mL: millilitres; RF: rheumatoid factor; SD: standard deviation; U: units.

Table IV. Incidence of treatment emergent adverse events (Safety set).

| | Safety set (n=273) |
|---|--------------------|
| <i>All values reported as n (%) [#], unless otherwise indicated</i> | |
| Any TEAEs | 66 (24.2) [91] |
| Severe TEAEs | 2 (0.7) [2] |
| Patient discontinuation due to TEAE | 16 (5.9) [22] |
| Drug-related TEAEs | 18 (6.6) [20] |
| Serious TEAEs | 18 (6.6) [22] |
| Malignancies | 3 (1.1) [3] |
| <i>Most common TEAEs^a by SOC</i> | |
| General disorders and administration site conditions | 32 (11.7) [35] |
| Drug ineffective ^b | 23 (8.4) [23] |
| Any local reaction ^c | 12 (4.4) [23] |
| Skin and subcutaneous tissue disorders | 11 (4.0) [15] |
| Psoriasis ^d | 4 (1.5) [4] |
| Rash ^d | 2 (0.7) [3] |
| Erythema ^d | 2 (0.7) [4] |
| Infections and infestations | 7 (2.6) [8] |
| Urinary tract infection ^d | 2 (0.7) [2] |
| Investigations | 6 (2.2) [6] |
| Hepatic enzyme increased ^d | 2 (0.7) [2] |
| Transaminases increased ^d | 2 (0.7) [2] |
| TEAEs leading to death | 2 (0.7) [3] |
| Sepsis | 1 (0.4) |
| Cardiac disorder | 1 (0.4) |

[#]: number of individual occurrences of the TEAE. ^aThe most common TEAEs are reported for system organ classes occurring in $\geq 2\%$ of patients. ^bThe most common general disorders and administration site conditions are reported by preferred term in $\geq 2\%$ of patients. ^cAny local reactions which occurred at the site of CZP administration were collected in addition to the MedDRA defined terms. ^dReported by preferred term. CZP: certolizumab pegol; MedDRA: Medical Dictionary of Regulatory Activities; SOC: system organ class; TEAE: treatment emergent adverse event.

related to the study drug. One patient died as a result of sepsis due to a urinary tract infection; the relationship to the study drug was unknown. The second patient experienced a cardiac disorder and myocardial necrosis; it was unknown whether an autopsy was conducted but the cause of death was considered as acute necrosis of the heart muscle and pulmonary origin cardiac disease.

Discussion

We demonstrate that there were no clinically relevant short-term associations of smoking history and CZP response in patients with RA, measured by change

in DAS28(ESR) from baseline to Week 12. Additionally, no significant long-term correlations were observed between baseline smoking history (measured by cigarette pack-year history) and DAS28(ESR) at all timepoints through Week 104. Similar trends were observed in the Hungarian and Czech cohorts when analysed separately. However, current smoking habits at Week 104 were significantly associated with a smaller DAS28(ESR) reduction from baseline for all countries. Although the association was significant, it was weak, and the clinical relevance of this association is not clear. This result opposes

that from previous reports (20, 28) and does not align with our observations at earlier timepoints. As the association is small (slope estimate = -0.068), we believe this finding to be arbitrary.

An association between current or past cigarette smoking and an increased risk of developing RA has been demonstrated in a number of case-control studies, including a survey-based study of disease-discordant twins (8, 9, 30-32). Prospective analyses from the Nurses' Health Study also demonstrated an association between smoking intensity and risk of RA, with the risk of RA increasing with the amount smoked (33); however, a meta-analysis concluded that this risk was not increased above 20 pack-years (34).

Despite previous reports from the ESPOIR and BARFOT cohort studies, that current smokers with RA had higher disease activity, and were less likely to be in remission at 12 months compared to non-smokers with RA (11, 35), the present study suggests that smoking history does not negatively impact CZP efficacy in patients with RA in these Central European countries. Overall, the results of the CIMDORA study support the observations made in the RENACER study, which assessed patients with RA from a Spanish multicenter national database, in which no differences in clinical response to CZP amongst active smokers were observed (28). Additionally, the proportions of Crohn's disease patients with a smoking history were similar between those experiencing successful or failed CZP treatment (36). The outcomes of our study are supported by a previous small-scale study, which reported no association between exposure to primary or passive smoking and efficacy of other anti-TNF treatments (infliximab, etanercept and adalimumab) (17). However, our results are unlike the findings from the majority of studies assessing other anti-TNF therapies, which have demonstrated reduced efficacy in patients with RA who smoke. For example, response to infliximab has been found to be inversely associated with increased cigarette pack-year history (19). Other trials showed that patients with early RA who were current smokers, were less likely

to respond well (>1.2 unit decrease in DAS28 from baseline) to the anti-TNF treatments infliximab, etanercept or adalimumab after three months, compared to those who had never smoked (20). Similarly, predictive modelling of anti-TNF discontinuations, within one year of initiation, showed that current smoking was a predictor for discontinuation, in a cohort of patients with RA treated with adalimumab, etanercept, infliximab, golimumab and CZP (13).

The reason for the disparity in observed efficacy of other anti-TNFs (infliximab, adalimumab and etanercept) (19, 20) and that of CZP in the present study in smokers and non-smokers is not clear. This could be a consequence of the PEGylated structure of CZP (21). The PEGylation of CZP changes the physical and chemical properties of the biologic molecule and increases the stability and retention time of CZP within the blood compared to non-PEGylated agents (37). This may inhibit the alteration in pharmacokinetics observed for other anti-TNFs taken by current smokers (21, 38, 39); however, as the present study did not investigate pharmacokinetics we cannot infer that this is the cause of our findings. An increased production of anti-CCP and/or RF has been observed in smokers (19), and these proteins have been implicated in the poor response to anti-TNFs (40), but RF production did not influence response to anti-TNF treatments in patients with RA (41). Therefore, since current and past smokers have higher levels of TNF- α (42), an alternative hypothesis is that these patients may require higher doses of anti-TNF therapies. The mechanisms behind the lack of effect of smoking on CZP efficacy are yet to be confirmed.

No new safety signals were identified during the study, which provides an overall positive benefit-risk ratio of long-term CZP treatment. This is in line with previous reports of CZP treatment in patients with RA of varying severities (23, 25, 26). Two deaths were reported during this study, both of which were considered unrelated to the study drug; however, as both patients had been taking CZP for more than 1 year prior to their death the related-

ness of these fatalities to CZP cannot be ruled out.

The limitations of this study include its observational and uncontrolled design, which introduced the potential for bias, although this is common to all such studies. Furthermore, any changes in DAS28(ESR) could only be correlated with self-reported smoking status, which may have been mis-reported by patients. Most patients (60.6%) enrolled into the study did not have a smoking history (*i.e.* pack-year history <1), which may have impacted on the results reported here, however, sensitivity analyses were not performed on the two groups of patients making up this cohort (patients who smoked <1 pack of cigarettes in a year, and patients who had never smoked). The distribution of patients was uneven across the participating countries, with 197 patients from Hungary, 55 patients from the Czech Republic, and only 21 patients from Slovakia. Cigarette pack-history was higher in the Hungarian than in the Czech patients. The relatively small patient population size was also a limitation, particularly for the individual analyses of each participating country. Also, as this was a local study, the results may not be transferrable to regions outside of these Central European countries. Furthermore, the primary analysis, of the association between the change in DAS28(ESR) data and smoking history was at Week 12, which is an early timepoint considering the length of the study.

Conclusion

In conclusion, during 104 weeks of CZP treatment, prior smoking status had no significant impact on the efficacy of CZP. The rapid therapeutic response to CZP treatment, established in previous studies, was maintained in Hungarian, Czech and Slovak patients with RA (23, 25, 26).

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