Three-year clinical outcomes in patients with rheumatoid arthritis treated with certolizumab pegol: results from the observational ECLAIR study

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Abstract

Objective

To describe the long-term effectiveness and safety of certolizumab pegol in patients with moderate-to-severe rheumatoid arthritis (RA) in a real-world setting in France.

Methods

ECLAIR was a 3-year longitudinal, prospective, observational, multicentre study. The primary objective was to describe the EULAR response after 1 year of certolizumab pegol treatment. Other endpoints included DAS28, clinical disease activity index, health assessment questionnaire disability index, fatigue assessment scale, patient's assessment of arthritis pain, patient and physician global assessments of disease activity, patient quality of life, and long-term safety.

Results

A total of 792 patients were enrolled, of whom 776 comprised the safety set, and 733 the full analysis set. In the full analysis set, 559, 469 and 430 patients had a 12-, 24- and 36-month visit, respectively. This included 378, 296 and 246 patients still receiving certolizumab pegol at these visits. The percentage of EULAR responders was 75.3% (305/405 patients with an available EULAR response) at 12, 76.5% (261/341) at 24, and 79.6% (226/284) at 36 months. Among those still receiving certolizumab pegol, the percentage of EULAR responders was 81.7% (237/290) at 12, 81.1% (185/228) at 24, and 87.3% (158/181) at 36 months. Sustained improvements were observed in other effectiveness outcomes. Overall, 45.1% (350/776) of patients experienced 776 adverse drug reactions. No new safety signals were identified.

Conclusion

This is the first prospective, observational study of an anti-TNF treatment in France. The results confirm the effectiveness and safety profile of certolizumab pegol treatment in patients with RA in a real-world setting.

Key words

rheumatoid arthritis, certolizumab pegol, TNF-α-inhibitor, DMARDs biologic, disease activity, observational study

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Introduction

Anti-tumour necrosis factor (anti-TNF) therapies have considerably changed the management of rheumatoid arthritis (RA) and have demonstrated efficacy in improving the signs and symptoms of disease, slowing the progression of functional and structural damage, and improving patient health-related quality of life (QoL), particularly when used in combination with methotrexate (MTX) (1, 2). Certolizumab pegol (CZP) is an Fc-free, PEGylated anti-TNF, with an enhanced half-life (approximately 14 days) allowing dosing every 2 or 4 weeks (3, 4). It has been approved for adult patients with moderate-to-severe active RA, in addition to those with psoriatic arthritis or axial spondyloarthritis (5).

The efficacy and safety of CZP in patients with active RA unresponsive to previous treatment were established in three randomised, placebo-controlled phase 3 trials (FAST4WARD [NCT00548834], RAPID 1 [NCT00152386] and RAPID 2 [NCT00175877]), in which CZP was administered with MTX or as monotherapy (6-8). The results from these studies demonstrated rapid and significant improvements in signs and symptoms of RA after 24 weeks of treatment. Long-term administration of CZP combined with MTX has been also assessed in patients with RA, and resulted in sustained inhibition of radiographic progression and improvements in clinical outcomes (9, 10).

However, the aforementioned clinical trials were conducted in patients with strict selection criteria, resulting in more homogeneous and less complex populations than those seen in routine clinical practice. Long-term observational data in more representative populations are therefore necessary, and are frequently considered or requested by health authorities. Several observational studies have previously reported on the effectiveness and safety of CZP in real-world settings in Canada, Germany and the UK, but an observational study of an anti-TNF has yet to be conducted in France (11-13). To this end, the French National Authority for Health requested an observational study to assess the effectiveness and safety of CZP up to 36 months in patients with moderate-to-severe RA in a real-world setting in France.

Methods

Study design

ECLAIR was a prospective, multicentre, longitudinal, non-interventional study conducted in France between 2011 and 2017. Study sites were randomly selected from an exhaustive list of hospital rheumatologists and internal medicine specialists who manage patients with RA.

During the inclusion period, each participating site was asked to include up to 20 consecutive patients meeting the selection criteria. Eligible patients were adults (aged ≥18 years) with moderate-to-severe active RA, starting treatment with CZP following inadequate response to other disease-modifying antirheumatic drugs (DMARDs; including MTX), who provided written consent to participate in the study. Given the non-interventional design of the study, the decision to treat patients with CZP was independent from the decision to enrol the patient in the study.

Demographic, clinical and health resource utilisation data were collected at the inclusion visit (baseline) and at follow-up visits scheduled in accordance with routine clinical practice, at approximately 3, 6, 12, 18, 24 and 36 months. The initial prescription of CZP, as well as the 12-, 24- and 36-month follow-up visits, were conducted by hospital rheumatologists or internal medicine specialists, while the 3-, 6-, and 18-month visits could be conducted either at a hospital (by hospital rheumatologists or internal medicine specialists), or by private rheumatologists or general practitioners (30 private rheumatologists and 1 general practitioner were involved in the study). Patients who discontinued CZP could remain in the study unless they decided to withdraw from the study.

Study procedures and evaluations

The primary effectiveness outcome was the European League Against Rheumatism (EULAR) response at 12 months, assessed by the Disease Activity Score-28 joint calculated with erythro-

cyte sedimentation rate (DAS28[ESR]) (14, 15). The definitions of a 'moderate' or 'good' EULAR response are described in Supplementary Table S1.

Secondary effectiveness outcomes included change from baseline in EULAR DAS28 response, DAS28, clinical disease activity index (CDAI), Health Assessment Questionnaire Disability Index (HAQ-DI), fatigue assessment scale (FASCA), patient's assessment of arthritis pain (PtAAP), and patient and physician global assessments of disease activity (PtGADA/PhGADA). Patient QoL was assessed at baseline and at each follow-up visit using the SF-36 and Qualisex questionnaires (16, 17). The latter was used only for a subset of patients, following a protocol amendment. The safety profile of CZP was also examined over the study period.

Statistical analysis

Safety analyses were conducted on the safety set (SS; all patients who received ≥1 dose CZP). As a conservative approach, all events for which the relationship with CZP was not documented were considered related to CZP. All other efficacy analyses were conducted on the full analysis set (FAS; all patients meeting the selection criteria, with no protocol deviations). All patients in the FAS who received CZP up to the 12-month visit were included in the 12-month completer set (12-MCS). Completer sets for 3, 6, 18, 24 and 36 months were defined using the same principle.

All variables were analysed using descriptive statistics. Supportive analyses were conducted for EULAR response. In the first approach, missing data were imputed using last observation carried forward (LOCF) or linear interpolation. A more conservative approach was also applied, in which patients who stopped CZP treatment before the 12-month visit were considered non-responders, and missing data at 12 months were imputed using LOCF or linear interpolation for patients who continued CZP.

Univariate and multivariate logistic regression analyses were conducted to identify prognostic factors for clinical response. Variables with a p-value ≤0.20 in univariate models were considered for multivariate logistic regression models. A stepwise procedure was used to test each potential predictor in the multivariate model adjusted by site, and those with a p-value ≤0.05 were retained. Interactions between all variables included in the multivariate model were tested.

SAS® software 9.2 (SAS institute, North Carolina, USA) was used for statistical analyses.

Ethical considerations

The study was conducted in accordance with the Good Epidemiology Practice guidelines, the ethical principles arising from the Declaration of Helsinki and all relevant French regulations. The study was submitted to the relevant authorities as per the regulations in force in 2011; it was approved by the advisory committee on the processing of health research information (CCTIRS) and authorised by the French National Commission for Data Processing and Privacy (CNIL).

Results

Patient disposition and baseline characteristics

In total, 176 investigators (170 hospital rheumatologists, 6 internal medicine specialists) enrolled 792 patients between 20 December 2011 and 23 December 2013, of whom 776 (98.0%) comprised the SS, and 733 (92.6%) the FAS. In the FAS, 559, 469 and 430 patients had a 12-, 24- and 36-month visit, respectively (including 378, 296 and 246 patients still receiving treatment with CZP) (Suppl. Fig. S1).

Baseline characteristics for the FAS are described in Table I. The vast majority of patients (99.5%) had previously been treated with a DMARD: 98.4% with conventional DMARDs (generally MTX: 94.7% [694/733]) and 33.0% with biological DMARDs (generally anti-TNF therapies: 30.4% [223/733]). The mean (SD) DAS28(ESR) score at baseline was 4.8 (1.3). Many patients had high disease activity according to the DAS28[ESR] score (41.0%) and according to the CDAI score (59.7%) as well. SF-36 and Qualisex scores revealed an impact of disease on patients' QoL at baseline.

The prescription modalities of CZP were in accordance with marketing authorisation: in the FAS, 90.7% [665/733] of patients received a loading dose of 400 mg at weeks 0, 2 and 4. At 3, 6, 12 and 18 months, respectively 98.5% (648/658), 97.1% (536/552), 96.7% (441/456), and 93.2% (328/352) of patients still undergoing treatment with CZP received a maintenance dose of 200 mg every 2 weeks (as did 86.9% [286/329] and 74.6% [209/280] of patients at 24 and 36 months, respectively). CZP was prescribed as monotherapy in 31.1% (228/733) of patients and in combination with other DMARDs in 68.9% (generally MTX: 57.8% [424/733]; median weekly dosage: 20.0 mg [Q1–Q3: 15.0–20.0]). Other concomitant medications included systemic corticosteroids (53.8% [394/733] of patients; median daily dose of equivalent prednisone: 10.0 mg [Q1–Q3: 5.0–15.0]), and non-steroidal anti-inflammatory drugs (NSAIDs) (35.2% [258/733] of patients).

At baseline, 34.2% (249/729) of patients in the FAS were in full-time employment, 8.6% (63/729) in part-time employment, and 57.2% (417/729) unemployed. The main reasons for unemployment were retirement (59.5% of unemployed patients), RA (20.6%) and housekeeping (7.2%). Among employed patients, 23.2% had missed days of paid work during the previous month, mainly because of RA (data not shown).

Effectiveness

In the FAS, the median duration of CZP treatment was 17.9 (Q1–Q3: 7.4–36.5) months. Kaplan-Meier analysis of CZP discontinuation estimated patient retention rates of 61.3% at 12 months (n=419), 48.7% at 24 months (n=306), and 42.4% at 36 months (n=133). At the 36-month visit, CZP treatment had been permanently discontinued for 64.8% (475/733) of patients with the main reasons for this being primary lack of response (34.8% [138/396]), secondary loss of response (19.2% [76/396]) and intolerance (18.7% [74/396]).

At the 12-month visit, the EULAR response was calculated in 405 out of 559 patients still in the study. Among them, 75.3% (95% CI: 70.9–79.3%) were

Table I. Baseline demographics and disease characteristics.

	FAS (n=733)
Age (years) at CZP treatment initiation (n=733), mean (SD)	55.1 (13.1)
Female, n (%)	572 (78.0)
Age (years) <40, n (%)	86 (11.7)
Age (years) ≥40 and <65, n (%)	361 (49.2)
Age (years) ≥65, n (%)	125 (17.1)
Weight (kg) (n=724), mean (SD)	68.7 (15.2)
BMI (kg/m^2) (n=716), mean (SD)	25.3 (5.1)
Duration of RA (years) (n=731), mean (SD)	8.8 (8.8)
Any prior DMARD treatment, n (%)[a]	729 (99.5)
Conventional DMARD	721 (98.4)
Methotrexate	*694 (94.7)*
Biologic DMARD	242 (33.0)
TNF inhibitors	*223 (30.4)*
Etanercept	165 (22.5)
Adalimumab	120 (16.4)
Infliximab	54 (7.4)
Golimumab	3 (0.4)
Number of prior DMARDs, n (%)	
0	4 (0.5)
1	132 (18.0)
2	163 (22.2)
≥3	434 (59.2)
Any DMARD treatment concomitant to CZP initiation, n (%)	505 (68.9)
Conventional DMARD	505 (68.9)
Methotrexate	424 (57.8)
Erythrocyte sedimentation rate (mm/hr) (n=670), mean (SD)	24.9 (22.1)
C-reactive protein (mg/L) (n=674), mean (SD)	13.4 (17.9)
Rheumatoid Factor positive, n (%)	267 (70.3)
Cyclic Citrullinated Peptide Antibody positive, n (%)	303 (76.1)
TJC[b] (n=724), mean (SD)	8.9 (7.1)
SJC[b] (n=722), mean (SD)	5.6 (5.1)
DAS28 (ESR)[c] (n=647), mean (SD)	4.8 (1.3)
DAS28[c] score, n (%)	
Low (score ≤3.2)	62 (9.6)
Moderate (3.2< score ≤5.1)	320 (49.5)
High (score >5.1)	265 (41.0)
CDAI score (n=700), mean (SD)	25.7 (12.3)
CDAI activity, n (%)	
Remission (≤2.8)	4 (0.6)
Low disease activity (>2.8 and ≤10)	48 (6.9)
Moderate disease activity (>10 and ≤22)	230 (32.9)
High disease activity (>22)	418 (59.7)
Fatigue[d] (n=680), mean (SD)	6.1 (2.2)
PtAAP[e] (mm) (n=706), mean (SD)	52.9 (23.6)
PhGADA[f] (mm) (n=727), mean (SD)	56.0 (18.7)
PtGADA[f] (mm) (n=715), mean (SD)	56.1 (22.3)
HAQ-DI total score (n=696), mean (SD)	1.28 (0.69)
HAQ-DI total score, n (%)	
High (score >0.5)	570 (81.9)
Low (score ≤0.5)	126 (18.1)
SF-36 scores (norm-based)[g]	
Mental Component Score (n=685), mean (SD)	37.91 (11.55)
Physical Component Score (n=685), mean (SD)	35.85 (8.19)
Qualisex total score[h] (n=115), mean (SD)	3.73 (2.77)
Female	4.06 (2.83)
Male	3.10 (2.56)
Age <40 years	3.05 (2.20)
Age ≥40 and <65 years	3.68 (2.84)
Age ≥65 years	4.42 (2.88)

a: Prior treatments included any initiated before the first dose of CZP (one patient may have received multiple prior treatments); b: 28-joint count, assessed within -8 days and +30 days of CZP treatment initiation; c: Based on the TJC, SJC, ESR and PtGADA; d: Measured using the FASCA, ranging from 0=no fatigue to 10=worst fatigue; e: Measured using a 100 mm visual analogue scale, ranging from 0=no pain to 100=severe pain; f: Measured using a 100 mm visual analogue scale, ranging from 0=very good, asymptomatic and no limitation of normal activities, to 100=very poor, very severe symptoms, which are intolerable, and inability to carry out all normal activities; g: Each score ranges from 0=maximum disability, to 100=no disability; h: Score ranges from 0=no impact of RA, to 10=full impact of RA.
BMI: body mass index; CDAI: clinical disease activity index; CZP: certolizumab pegol; DAS28: 28-joint disease activity score; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; FAS: full analysis set; FASCA: fatigue assessment scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; PhGADA: Physician's Global Assessment of Disease Activity; PtAAP: Patient's Assessment of Arthritis Pain; PtGADA: Patient's Global Assessment of Disease Activity; RA: rheumatoid arthritis; SD: standard deviation; SF-36: 36-item short-form health survey; SJC: swollen joint count; TJC: tender joint count.

classified as responders (Fig. 1). This included 48.6% of patients who were classified as 'good' responders (95% CI: 43.8–53.5%) and 26.7% 'moderate' responders (95% CI: 22.5–31.1%). The remaining patients (24.7%) were classified as non-responders (95% CI: 20.7–29.1%).

The proportion of EULAR responders at the 12-month visit was higher in patients who were anti-TNF-naïve prior to CZP initiation (81.3%, 95% CI: 76.6–85.4%) compared to those who were experienced (58.1%, 95% CI: 48.5–67.2%), and in those with concomitant MTX use at baseline (79.9%, 95% CI: 74.6–84.6%) *versus* those without (68.3%, 95% CI: 60.9–75.1%). Univariate and multivariate logistic regression analyses conducted in the FAS, using imputation by linear interpolation/LOCF and/or non-response imputation, and adjusted for centre, showed that high or moderate DAS28 scores and concomitant DMARD use at CZP initiation were positive predictors of clinical response at the 12-month visit (odds ratios [OR]: 17.6, 4.5, and 3.3, respectively) and increased fatigue score was a negative predictor of clinical response at the 12-month visit (OR: 0.8 for a 1-mm increase in fatigue score) (Fig. 2).

Among the patients with on-going CZP treatment at 12 months (12-MCS; n=378), the EULAR response was calculated in 290 patients: 81.7% (95% CI: 77.0–85.8%) were responders ('good' responders: 56.2% [95% CI: 50.5–61.8%]; 'moderate' responders: 25.5% [95% CI: 20.8–30.8%]) and 18.3% were non-responders (95% CI: 14.2–23.0%). Prognostic factors of EULAR response at the 12-month visit assessed in the 12-MCS are provided in Supplementary Figure S2. Concomitant DMARD use at baseline was common among patients with on-going CZP treatment at 12 months (74.6% [282/378]) and generally was with MTX (63.5% [240/378]). Use of concomitant DMARDs at baseline was similar in the 12-month documented set (72.5% [405/559]) with MTX again the most common concomitant treatment (60.5% [338/559]).

Supportive analyses conducted in the FAS for EULAR response are presented in Table II. Following a con-

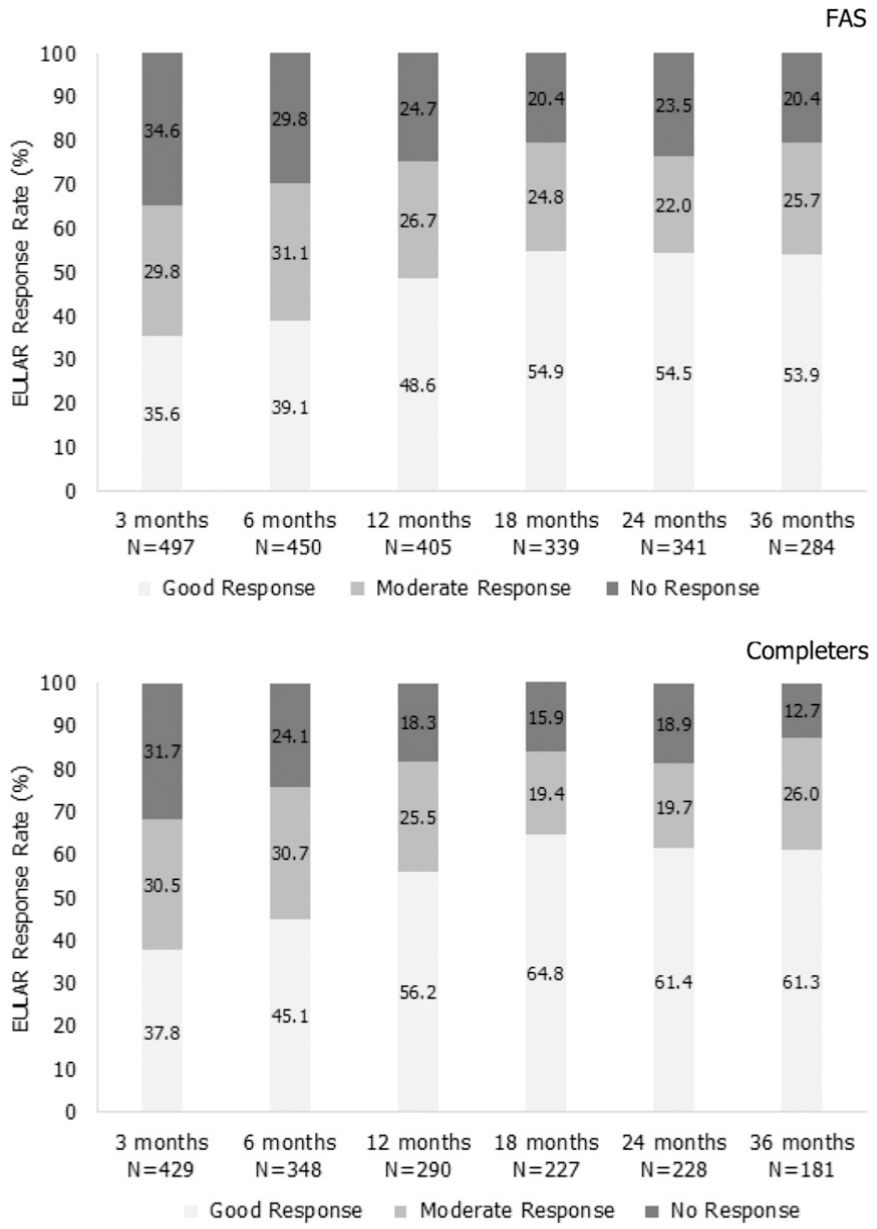

Fig. 1. EULAR response over 36 months of follow-up.

servative approach, in which patients who stopped CZP treatment before the 12-month visit were considered non-responders (remaining missing data at the 12-month visit were imputed using LOCF or linear interpolation), the percentage of EULAR responders at the 12-month visit was calculated as 44.3% (95% CI: 40.6–48.1%). Use of a more conservative approach, in which all patients who stopped CZP treatment were considered non-responders (non-responder imputation), the percentage of EULAR responders at 12-months was calculated as 41.6% (305/733).

The proportion of EULAR responders over time is presented for patients still in the study and for the completer sets in Figure 1. In the FAS, the proportion of EULAR responders was 76.5% (261/341 patients with an available EULAR response) at the 24-month visit, and 79.6% (226/284 patients with an available EULAR response) at the 36-month visit. The majority of responders met the criteria for a 'good' EULAR response. Supportive analysis, using non-responder imputation, calculated the percentage of EULAR responders at the 24-month and 36-month visit to be 35.6% (261/733) and 30.8% (226/733), respectively.

Among the patients still in the study, the proportion of patients who achieved EULAR remission (DAS28 <2.6) was 44.0% (193/439 patients with an available DAS28 score) at the 12-month visit, 48.5% (172/355 patients with an available DAS28 score) at the 24-month visit and 50.7% (153/302 patients with an available DAS28 score) at the 36-month visit (data not shown).

Consistent with the EULAR response, the mean CDAI score decreased from baseline among patients from the FAS (Table III). Reductions in fatigue were also reported by patients throughout the follow-up period, along with decreases in physical function (assessed by the HAQ-DI), arthritis pain, and Pt/PhGA-DA scores (Table III). Improvements in QoL scores were also evident over the study period, with a sustained increase in mean SF-36 scores (physical and mental components), and a small decline in mean Qualisex score among patients for whom this was measured (Table III).

Health resource utilisation

In the FAS, healthcare provider (HCP) consultations were mainly performed by rheumatologists and general practitioners. The observed proportion of patients attending HCP visits related to RA decreased with time, as did the proportion with medical procedures (Suppl. Table S2). Similarly, the observed proportion visiting the emergency room (ER) or requiring hospitalisations >1 day in length tended to decrease between the 12-month and the 24-month visit and was maintained to the 36-month visit (Suppl. Table S2).

Safety

Safety data are summarised for the SS (n=776) in Table IV. Overall, 431 (55.5%) patients experienced a total of 1,184 adverse events. A total of 237 patients (30.5%) experienced adverse events leading to drug discontinuation. Five deaths (0.6%) were reported over the course of the study: 3 patients died from cancer (2 considered not related to CZP, 1 causality not available), 1 patient from myocardial infarction (considered not related to CZP), and there was 1 unspecified death (considered

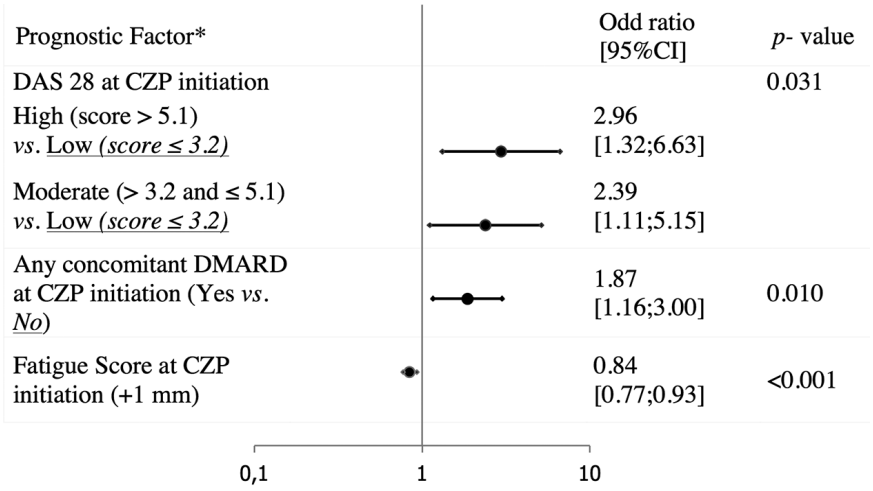

Fig. 2. Prognostic factors for EULAR response at 12 months (FAS).

Table II. EULAR response at 12 months.

		12-MDS (n=559)	12-MCS (n=378)	FAS (n=733)	FAS (n=733)
	n	405	290	591	681
	Missing values Imputation	154 None	88 None	142 Linear interpolation + LOCF	52 NRI + linear interpolation + LOCF
No EULAR response	n (%) [95% CI]	100 (24.7) [20.7;29.1]	53 (18.3) [14.2;23.0]	180 (30.5) [26.8;34.3]	379 (55.7) [51.9;59.4]
EULAR response	n (%) [95% CI]	305 (75.3) [70.9;79.3]	237 (81.7) [77.0;85.8]	411 (69.5) [65.7;73.2]	302 (44.3) [40.6;48.1]
Good	*n (%)* *[95% CI]*	*197 (48.6)* *[43.8;53.5]*	*163 (56.2)* *[50.5;61.8]*		
Moderate	*n (%)* *[95% CI]*	*108 (26.7)* *[22.5;31.1]*	*74 (25.5)* *[20.8;30.8]*		

12-MCS: 12-month completer set; 12-MDS: 12-month documented set; CI: confidence interval; EULAR: European League Against Rheumatism; FAS: Full Analysis Set; LOCF: last observation carried forward; NRI: non-response imputation.

related to CZP). The latter was in a patient with subarachnoid haemorrhage and ruptured cerebral aneurysm, which were reported after treatment stop and considered not related to CZP; the patient experienced complications including lung infection, bacterial meningitis and septic shock, which were considered related to CZP.

Overall, 350 patients (45.1%) experienced a total of 776 events with suspected relationship to CZP (adverse drug reactions [ADRs]; Table IV). Among them, 242 serious ADRs were experienced by 151 patients (19.5%; Incidence rate [IR]: 10.2 per 100 patient-years). The most frequent serious ADRs were infections and infestations (8.6%), skin and subcutaneous tissue disorders (2.4%), respiratory, thoracic and mediastinal disorders (2.4%), and musculoskeletal and connective tissue disorders (2.1%). Serious ADRs that occurred in ≥1% of patients were psoriasis (1.2%), herpes zoster (1.0%), and hepatocellular injury (1.0%).

In addition, 13.1% of patients experienced a total of 135 adverse events of special interest (AESIs) (Table IV). No serious skin reactions were reported. Four cases of tuberculosis (including disseminated tuberculosis and pulmonary tuberculosis) were reported. One case occurred during CZP treatment, two after CZP discontinuation, and one at an unknown date. Treatments for tuberculosis were reported in 3 patients and were unknown for 1 patient.

Discussion

ECLAIR was the first prospective, observational study of an anti-TNF conducted in France. The aim was to describe disease outcomes in patients with RA treated with CZP in a real-world setting, in response to a request from the French National Authority for Health to provide complementary data to clinical trials. ECLAIR builds on previous real-world observational studies into the effectiveness of CZP which have been conducted in other countries (11-13).

The aim of CZP therapy is to reduce disease activity and prevent disease flare; if the patient is not suffering any adverse reactions to treatment and their disease is stable, their treatment regimen would not be changed. Therefore, as CZP is recommended for use with concomitant MTX treatment, a reduction in MTX use would not be expected. Corticosteroids are recommended only for patients during early treatment phases while DMARDS are taking effect and following disease flare. Once remission is achieved patients will be tapered from corticosteroids. As CZP therapy demonstrates superior efficacy to traditional DMARDs alone, both at achieving remission and reducing flares, corticosteroid use would be expected to be lower in this group.

By including patients who are not typically enrolled in clinical trials (*e.g.* those with chronic or serious comorbidities, early or late disease, or prior biologic use), observational studies generate data that are generalisable to the wider patient population (18). In order to enrol a cohort that was representative of the population of RA patients treated with CZP in France, sites were randomly selected from an exhaustive list of those treating patients with RA. To prevent selection bias, investigators were asked to consecutively enrol eligible patients in chronological order of their arrival at the site, and based solely on their fulfilment of selection criteria.

The demographic characteristics of patients enrolled in ECLAIR were comparable to those in clinical trials (RAPID

Table III. Impact of CZP and on clinical and quality-of-life outcomes at 12, 24 and 36 months.

	Baseline[a]		12 months[b]		Change from baseline		24 months[b]		Change from baseline		36 months[b]		Change from baseline	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
CDAI	700	25.7 (12.3)	502	11.2 (11.1)	494	-13.9 (13.0)	402	9.3 (9.8)	394	-15.5 (13.4)	346	8.8 (10.0)	339	-15.9 (13.6)
Fatigue[c]	680	6.1 (2.2)	461	4.8 (2.5)	438	-1.3 (2.5)	385	4.6 (2.6)	362	-1.3 (2.7)	303	4.6 (2.6)	285	-1.3 (2.8)
HAQ-DI	696	1.3 (0.7)	466	0.8 (0.7)	449	-0.4 (0.6)	382	0.8 (0.7)	366	-0.4 (0.6)	307	0.8 (0.7)	295	-0.4 (0.7)
PtAAP[d]	706	52.9 (23.6)	511	30.7 (25.0)	496	-20.1 (28.2)	417	27.3 (23.9)	407	-23.1 (29.2)	363	27.6 (25.8)	353	-22.4 (30.5)
PhGADA[e]	727	56.0 (18.7)	532	25.8 (22.8)	530	-29.4 (26.0)	429	22.2 (21.2)	426	-33.0 (26.4)	389	21.7 (22.7)	388	-33.4 (26.6)
PtGADA[e]	715	56.1 (22.3)	514	32.4 (25.0)	506	-22.1 (28.2)	421	28.9 (23.5)	414	-24.7 (29.0)	363	28.2 (25.0)	357	-24.9 (29.2)
SF-36 scores (norm-based)[f]														
MC Score	685	37.9 (11.6)	454	42.6 (11.7)	431	3.9 (11.2)	379	44.0 (11.5)	360	4.7 (11.5)	301	43.8 (12.1)	285	4.7 (12.0)
PC Score	685	35.9 (8.2)	454	42.2 (9.7)	431	5.8 (8.8)	379	42.7 (10.0)	360	6.3 (9.2)	301	43.3 (10.5)	285	6.5 (10.0)
Qualisex total score[g]	115	3.7 (2.8)	77	2.8 (2.8)	52	-0.4 (1.7)	51	3.0 (2.8)	39	0.0 (2.3)	47	2.5 (2.4)	31	-0.3 (2.0)

a: Full analysis set; b: Observed data from patients from the FAS still in the study at each timepoint; c: Measured using the FASCA, ranging from 0=no fatigue to 10=worst fatigue; d: Measured using a 100 mm visual analogue scale, ranging from 0=no pain to 100=severe pain; e: Measured using a 100 mm visual analogue scale, ranging from 0=very good, asymptomatic and no limitation of normal activities, to 100=very poor, very severe symptoms, which are intolerable, and inability to carry out all normal activities; f: Score from 0 (maximum disability) to 100 (no disability); g: Score from 0 (no impact of RA) to 10 (full impact of RA).
CDAI: clinical disease activity index; CZP: certolizumab pegol; FASCA: fatigue assessment scale; HAQ-DI: health assessment questionnaire-disability index; MC score: Mental Component Score; PC score: Physical Component Score; PtAAP: Patient's Assessment of Arthritis Pain; PhGADA: Physician's Global Assessment of Disease Activity; PtGADA: Patient's Global Assessment of Disease Activity; SD: standard deviation.

1, RAPID 2 and FAST4WARD) (6, 8, 9). However, major differences should be highlighted. Specifically, the mean duration of RA in this study was longer than in RAPID 1 and 2 (8.8 years *vs*. 6.1 and 6.2 years, respectively). Nevertheless, mean DAS28 and HAQ-DI scores at baseline were lower in ECLAIR (4.8 and 1.3, respectively) than in RAPID 1 (6.9 and 1.5) or RAPID 2 (6.8 and 1.7). Patients enrolled in the trials thus had more severe disease, with more rapid progression, than those included in our study. In addition, 30.4% of patients included in ECLAIR had prior anti-TNF treatment – much higher than the proportions in RAPID 1 and 2 (4% and 5%, respectively) – and more than half (57.8%) of patients in ECLAIR received CZP in combination with MTX (31.1% as monotherapy). In comparison, all patients in RAPID 1 and 2 were treated with concomitant MTX, whereas all patients in the FAST4WARD received CZP as monotherapy.

Our results revealed rapid and sustained improvements in disease activity following CZP treatment initiation. The majority of patients achieved a EULAR response within 12 months (75.3%), which was sustained to 36 months among patients still in the study. Similar improvements in disease activity have been observed in previous observational studies into the long-term effectiveness of CZP (11-13). However, the EULAR response rate in ECLAIR was lower compared to the RAPID 1 study (96.2% at 12 months), which is likely due to higher baseline disease activity in the latter. Interestingly, we found high and moderate DAS28 scores to be positive predictors of EULAR response at 12 months in multivariate analyses.

In line with results observed in RAPID 1 and 2, we measured rapid improvements in patient-reported outcomes following treatment with CZP, including pain, fatigue, physical function, PtGADA, and overall health-related QoL (10, 19). The mean Qualisex score at baseline was comparable to that observed in the validation study conducted by Gossec *et al*. (16). Consistent with this study, our results may suggest a greater impact of RA on sex life in females than in males. Interestingly, the current study also suggests that the impact of RA on sex life tends to increase with age. However, the number of Qualisex questionnaires completed during follow-up was limited, reducing the power of these analyses. Thus, the improvement that we observed at 12 months should be further investigated.

Our results also highlight the negative impact of RA on patients' working lives, and are consistent with correlations reported in the literature between functional disability and radiographic joint damage, and employment status (20, 21). Additionally, our results suggest a decline in health resource utilisation over time, including physician visits, ER visits and medical procedures. Further investigations are needed, however, to confirm the impact of CZP on health resource utilisation, and compare this with other treatment regimens.

No new safety signals were observed over the course of the 3-year treatment period, and incidences of adverse events were consistent with other long-term evaluations of CZP (10, 22). Nine pregnancies were reported during the study and single events of abortion spontaneous, foetal distress syndrome, premature baby and premature delivery were observed, although not all pregnancy outcomes were reported, overall no new safety signals were observed.

Although persistence rates in ECLAIR (12-month retention rate: 61.3%) were lower than those observed in randomised clinical trials (10, 18), they were consistent with the retention rate described in a French database study by Belhassen *et al*. (12-month retention rate: 60.3) and in UK non-interventional study by Kumar *et al*. (Week 88 retention rate: 68.5%) (13, 23). Notwithstanding, treatment persistence is often better in clinical trials than it is in real-world clinical practice, mainly due to differences in terms of disease sever-

Table IV. Safety outcomes.

	Safety population n=776		
	Ne	n (%)	Incidence rate (per 100 patient-years)
Adverse drug reactions	**776**	**350 (45.1%)**	**32.4**
Infections and infestations	268	179 (23.1%)	13.1
Bronchitis	50	47 (6.1%)	2.9
Urinary tract infection	20	20 (2.6%)	1.2
Sinusitis	15	15 (1.9%)	0.9
Nasopharyngitis	15	14 (1.8%)	0.8
Oral herpes	11	11 (1.4%)	0.7
General disorders and administration site conditions	84	65 (8.4%)	4.1
Skin and subcutaneous tissue disorders	85	61 (7.9%)	3.8
Gastrointestinal disorders	51	40 (5.2%)	2.4
Respiratory, thoracic and mediastinal disorders	46	39 (5.0%)	2.4
Pregnancy, puerperium and perinatal conditions	13	9 (1.2%)	0.5
Pregnancy	9	9 (1.2%)	0.5
Serious adverse drug reactions	**242**	**151 (19.5%)**	**10.2**
Infections and infestations	83	67 (8.6%)	4.2
Herpes zoster	8	8 (1.0%)	0.5
Bronchitis	7	7 (0.9%)	0.4
Lung infection	7	7 (0.9%)	0.4
Pyelonephritis	7	7 (0.9%)	0.4
Candida infection	4	3 (0.4%)	0.2
Skin and subcutaneous tissue disorders	23	19 (2.4%)	1.1
Respiratory, thoracic and mediastinal disorders	22	19 (2.4%)	1.1
Musculoskeletal and connective tissue disorders	18	16 (2.1%)	1.0
Hepatobiliary disorders	11	11 (1.4%)	0.7
Deaths	**5**	**5 (0.6%)**	**0.3**
Adverse event of special interest	**135**	**102 (13.1%)**	**6.6**
Serious infections (excluding opportunistic infections)	77	62 (8.0%)	3.9
Tuberculosis	2	2 (0.3%)	0.1
Disseminated tuberculosis	1	1 (0.1%)	0.1
Pulmonary tuberculosis	1	1 (0.1%)	0.1
Malignancies	21	20 (2.6%)	1.2
Serious hemorrhages	9	7 (0.9%)	0.4

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Incidence rate was defined as the number of cases divided by study time of all patients who were at risk for the event; study time was defined as time from CZP initiation to the end of the study (for patients with no event), or time from CZP initiation to the first event (for patients with ≥1 event). Ne: number of events.

ity, comorbidities, treatment patterns or study monitoring (24, 25).

There are several limitations to our study. In the absence of randomisation, selection bias and confounding factors are shortcomings of all observational studies, including ours. However, results from observational studies are usually applicable to much broader populations and are a better picture of patterns in real-world practice. As such, direct comparisons between results of clinical trials and observational studies should be made with caution. However, generalisability of our results might be compromised by the selection of patients in the study. Participation in our study was voluntary, both for physicians and patients, which introduces an immediate response bias. Furthermore, although physicians were asked to enrol consecutive patients who met the selection criteria, factors such as health status, adherence to treatments, or the duration of study follow-up may have influenced enrolment decisions (by either party). Another limitation, which concerns every long-term observational study, is the extent of loss to follow-up. If dropouts did not occur randomly, patients who discontinued before the end of the study may differ from those who completed the study, which is likely to bias the study's results towards higher effectiveness over time. In order to reduce the rate of loss to follow-up, patients in our study were contacted twice a year throughout the study period by an independent company, either to remind them of the date of study visits, or if applicable, to collect reasons for withdrawal.

In summary, this was the first prospective, observational study conducted in RA patients treated with CZP in France. The results confirm the effectiveness of CZP – both in terms of clinical and patient-reported outcomes – in a real-world setting, and also provide insight on healthcare resource consumption in these patients. After three years of follow-up, no new safety signals were identified, with a safety profile that was consistent with randomised controlled trials.

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Data sharing statement

The datasets generated and analysed during this study are available in anonymised format upon reasonable request via the CSDR platform (http://www.clinicalstudydatarequest.com).

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