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SYSTEMATIC REVIEW

# Safety Profile of Certolizumab Pegol in Patients with Immune-Mediated Inflammatory Diseases: A Systematic Review and Meta-Analysis

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**Abstract**

*Introduction* Certolizumab pegol (CZP), an anti-tumor necrosis factor PEGylated Fab' fragment of a humanized monoclonal antibody, is currently approved for treatment of some immune-mediated inflammatory diseases (IMIDs). To our knowledge, no systematic review and meta-analysis evaluating the overall safety profile of CZP has been performed.

*Objective* The objective of this systematic review was to assess the adverse event (AE) patterns of CZP versus a control in patients with IMIDs.

*Methods* A systematic literature search was performed using PubMed/MEDLINE, EMBASE, the Cochrane Library, and the FDA database for clinical trials up to March 2014. Eligible studies were those that compared the safety profile of CZP to a control group in patients with IMIDs. The following data were extracted: number of patients experiencing AEs, serious AEs (SAEs), adverse drug reactions (ADRs), withdrawals due to AEs, fatal AEs, infectious AEs and SAEs, upper respiratory tract infections, injection-site reactions, neoplasms, and tuberculosis.

*Results* A total of 2023 references were identified and 18 randomized controlled trials were included. The main pooled risk ratios of CZP-treated versus control patients were as follows: AEs 1.09 (95 % confidence interval, CI 1.04–1.14), SAEs 1.50 (95 % CI 1.21–1.86), ADRs 1.20 (95 % CI 1.03–1.39), infectious AEs 1.28 (95 % CI 1.13–1.45), infectious SAEs 2.17 (95 % CI 1.36–3.47), and upper respiratory tract infections 1.34 (95 % CI 1.15–1.57).

*Conclusion* Safety data on CZP suggest an overall favorable tolerability profile, with infections being the most common AE. However, CZP-treated patients had a twofold higher risk of infectious SAEs than control patients. Large observational studies and data from national registries are needed to detect rare AEs, which might occur after long-term exposures to CZP.

**Key Points**

Safety data on certolizumab pegol (CZP) show an overall favorable tolerability profile.

The most commonly reported adverse effects associated with CZP are infections, with a twofold higher risk of serious infections.

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## 1 Introduction

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that plays a pivotal role in the pathogenesis of various diseases involving the immune system, such as Crohn's disease (CD), ulcerative colitis, rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and psoriasis. The pathogenesis of these immune-mediated inflammatory diseases (IMIDs) remains unknown. However, TNF has emerged as a key regulator of inflammatory processes, through the control of the expression of other pro-inflammatory cytokines, such as interleukin-1 and interleukin-6, and has become a key target for therapeutic interventions against diseases characterized by redundant cytokine environments, such as IMIDs [1].

The beginning of the 2000s has seen the transition from aspecific immunomodulators to biotherapies that specifically target cytokines (TNF, interleukins) or immune cells (T and B lymphocytes) implicated in the pathogenesis of immune diseases, with considerable improvement of treatment efficacy. At present, the main purpose of immune disease therapy is to reduce the disease activity to a very low level or even to achieve remission. In particular, the reduction of TNF levels has been shown to improve signs and symptoms of RA and other immune-mediated diseases, such as CD [2] or spondyloarthritis [3], and the development of TNF inhibitors has revolutionized the treatment of these illnesses.

Biological drugs employed to treat IMIDs include a class of specific agents that selectively bind TNF and inactivate TNF-dependent downstream activation of inflammatory pathways. Anti-TNF drugs comprise one TNF-receptor fusion protein (etanercept), three monoclonal antibodies (infliximab, adalimumab, and golimumab) and one pegylated Fab' (certolizumab pegol, CZP), and are currently approved for the medical management of various IMIDs [4].

In September 2007, Switzerland was the first country worldwide to approve CZP for treatment of active CD in patients with insufficient response to conventional therapy [5], followed by US Food and Drug Administration (FDA) approval in April 2008 for the same indication. CZP also received European Medicines Agency (EMA) and FDA approval for treatment of moderate to severe active RA (2009), severe active axSpA (2013), and active PsA (2013). The standard adult maintenance dose is 200 mg given subcutaneously every 2 weeks, or 400 mg every 4 weeks.

CZP differs from the other anti-TNF drugs by its structure, consisting of the Fab' antigen-binding domain of a humanized monoclonal anti-TNF antibody, which has been combined with polyethylene glycol (PEG) to increase its plasma half-life and thereby reduce its dosing frequency [6]. Consisting of a single Fab' domain and being devoid of the Fc region, CZP does not form multimeric immune complexes, does not activate complement, and does not induce antibody-dependent cell cytotoxicity. Of note, the lack of complement fixation on immune cells expressing TNF has been predicted to reduce the overall risk of infections [7]. However, even though pre-authorization trials on patients with RA and CD have shown a favorable safety profile of CZP, they also displayed an increased incidence of serious infections versus controls, mainly among patients with RA [8, 9].

To date, the available systematic reviews or meta-analyses assessing the tolerability profile of CZP have been carried out only in RA or CD patients. On this basis, the aim of the present study was to perform a systematic review and meta-analysis of the literature to provide an assessment of the overall safety profile of CZP in patients with IMIDs, including studies evaluating CZP in patients with RA, CD, axSpA, PsA, and psoriasis.

## 2 Methods

The methodology of this review conformed with PRISMA guidelines [10].

### 2.1 Article Inclusion Criteria

Eligible studies for inclusion were randomized controlled trials (RCTs; phase II, III, and IV) or cohort studies, where CZP was administered as a single agent or in combination with other therapies such as disease-modifying anti-rheumatic drugs (DMARDs). Studies that compared CZP to a control treatment, such as placebo or the same medications allowed for the experimental arm, were included. Studies that did not report safety data on CZP were excluded. No restrictions on the study population were imposed. Studies reporting aggregated safety data from populations exposed to different anti-TNFs, including CZP, from which individual CZP data could not be retrieved, were also excluded.

### 2.2 Search Strategy and Selection of Studies

We performed a systematic literature search using PubMed/MEDLINE, EMBASE, and the Cochrane Library up to March 2014 without language restrictions. We limited our search to articles published after 1 January 2002, i.e., the date that Choy and colleagues first presented data on the efficacy of CZP in humans [11]. The search strategy was developed and conducted by two authors (ACS and SM). Search terms included certolizumab or its trade name Cimzia® (UCB Pharma S.A., Brussels, Belgium) or its

study drug code CDP870, combined with safety, adverse reaction(s) or effect(s) or event(s), side effect(s), drug(-) induced or related, toxicity, toxic effect(s). The search was limited to humans. We also searched the ClinicalTrials.gov database for completed but unpublished studies, and the EMA and FDA websites to obtain details on study characteristics or outcomes, if these data were missing or unclearly presented in the original studies. We contacted study authors in order to acquire additional information in only one case, but no further data could be obtained.

Each title and abstract was reviewed independently by two authors (ACS and SM) in order to determine whether the paper was relevant to the review topic. For all potentially eligible references, the full text was obtained and the studies were included if they met the pre-specified inclusion criteria. The reference lists of retrieved articles were also reviewed for identifying additional relevant studies. Disagreements were resolved by discussion.

### 2.3 Data Extraction and Definition of Safety Outcomes

Two independent authors (ACS and ER) performed the extraction of data. Any disagreement was resolved by consensus or through intervention by a third author (SM) with a further review of full-text information. The following information was collected from each study: publication date; study name; first author's last name; year of publication; study design; number of participants and population characteristics; and intervention variables (including dosage and concomitant treatment). Since we were interested in the safety profiles of CZP for the approved dosages of 200 and 400 mg, we did not extract data from treatment arms with CZP 100 mg. In the present systematic review, we examined the following safety outcomes: (1) number of patients with at least one adverse event (AE) according to the definition of the World Health Organization [12]; (2) number of patients with at least one serious AE (SAE), defined as any events resulting in death, a life-threatening event, hospitalization/prolongation of ongoing hospitalization, persistent or significant disability/incapacity, or congenital abnormality/birth defect; (3) number of patients with at least one adverse drug reaction (ADR), defined as any event possibly related to treatment by investigators; (4) withdrawals due to AEs; (5) number of deaths (fatal AEs); (6) number of patients with at least one infectious AE; (7) number of patients with at least one infectious SAE, defined as infections associated with death, hospitalization, and use of intravenous antibiotics; (8) number of patients with at least one upper respiratory tract infection; (9) number of patients with at least one injection-site reaction; (10) number of patients with neoplasms, including benign and malignant tumors; and (11) number of patients with new diagnosis or reactivation of tuberculosis. From each study, we collected the definitions of CZP-related events for each safety outcome and compared them to our definitions of outcome. Indeed, from the extracted data, the number of patients experiencing the events of interest was consistent with our definitions of the safety outcomes.

Moreover, in consideration of our interest in evaluating possible differences in the CZP safety profiles between 200 and 400 mg for each clinical indication, we assessed these CZP groups (200 and 400 mg) separately.

### 2.4 Risk of Bias of Included Studies

The reviewers assessed the risk of bias of included studies by means of the Cochrane Collaboration's handbook, based on the following key domains: sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other sources of bias [13]. Every domain could be classified as high (inadequate) or low (adequate) risk of bias, or unclear if insufficient information were reported. In particular, for the evaluation of attrition bias, we excluded patients who withdrew from the studies for safety reasons. In addition, we considered the switching of non-responders from placebo to the experimental group to be another source of bias. We judged a study to have a low risk of bias if switching was not allowed; by contrast, a high risk of bias was assigned to studies where non-responders in the placebo arm were treated with CZP because of a possible under-estimation of risk ratio (RR) evaluations for all safety outcomes. Studies with adequate procedures in all domains were considered to display a low risk of bias, the ones with inadequate procedures in one or more domains were considered to be at high risk of bias, and those with unclear procedures in one or more domains were considered to be at unclear risk of bias. Of note, the quality criteria for cohort studies are not addressed here, since the selection process did not identify any cohort studies. Disagreements among reviewers were discussed and agreement was reached by consensus.

### 2.5 Statistical Analysis

The results were summarized in a meta-analysis using the inverse variance method. Data were pooled using the random-effects model, as described by DerSimonian and Laird [14]. We preferred to apply the random-effects model rather than the fixed-effects model since it incorporates intra- and inter-study variability such as clinical (i.e.,

patients with different background disease and CZP dosage 200 or 400 mg) and methodological (i.e., randomization method, etc.) diversity. Pooled data were expressed as RR with 95 % confidence intervals (CIs). We estimated the risk of AEs, SAEs, ADRs, withdrawal due to AEs, fatal AEs, infectious AEs and SAEs, upper respiratory tract infections, injection-site reactions, neoplasm, and tuberculosis by first considering CZP-treated patients versus control overall and then the 200 and 400 mg groups separately, in order to evaluate the effect of CZP dose. Of note, in the overall analysis studies with two comparisons, CZP 200 and 400 mg groups (both cases and total patients) were pooled to create a single pair-wise comparison versus control in order to avoid double counting of patients in the control group. Moreover, we performed a subgroup analysis with the aim of assessing the impact of underlying disease by calculating the RRs of all safety outcomes for all therapeutic indications according to CZP dosages (200 and 400 mg).

Heterogeneity was evaluated using the Chi-square ($\chi^2$) test and $I^2$ statistics, which estimate variability among the included studies (or inter-studies) rather than variability within studies (intra-study). An $I^2$ greater than 40 % was considered significant for heterogeneity [15]. However, an important issue of $I^2$ is that the test has high power to detect a small amount of heterogeneity mainly in the presence of large sample size studies, which may not be clinically relevant [16]. Therefore, we also estimated heterogeneity considering $\tau^2$, as described by DerSimonian and Laird, which is a measure of inter-study variability that does not systematically increase with either the number or size of studies in a meta-analysis [14, 16]. Of note, values of $\tau^2$ close to zero indicate high homogeneity between studies. We also performed meta-regression analyses to appraise the impact of dosage and disease on safety outcomes. Meta-regression was performed only when at least ten studies were available for each comparison [15]. All analyses were carried out with Review Manager (RevMan 5) software version 5.3 (Cochrane Collaboration, Oxford, UK) and STATA® version 10.1 (StataCorp LP, College Station, TX, USA).

## 3 Results

### 3.1 Search Results and Selection of Studies

The identification process allowed retrieval of 2023 references. After removing duplicates, the number of references was 1630. The subsequent screening phase identified 179 publications reporting the results of eligible studies. Full-text papers were evaluated for eligibility, and 18 RCTs met the inclusion criteria. No cohort study was included due to the lack of control groups. Data were extracted from the 18 included studies (Fig. 1). Eleven studies were conducted in RA patients (one phase II/III; nine phase III; one phase IV) [17–27], four in CD patients (one phase II; three phase III) [6, 28–30], one in axSpA patients [31], one in PsA patients [32], and one in psoriasis patients [33].

### 3.2 Study Characteristics

All 18 studies were multicenter, randomized, placebo-controlled trials, assessing the efficacy and safety of CZP as induction or maintenance therapy. Among them, 17 studies were double-blind [6, 17–20, 22–33] and one study was single-blind [21]. With regard to patient age, subjects with CD (mean age 37.5 years), axSpA (mean age 39.6 years)

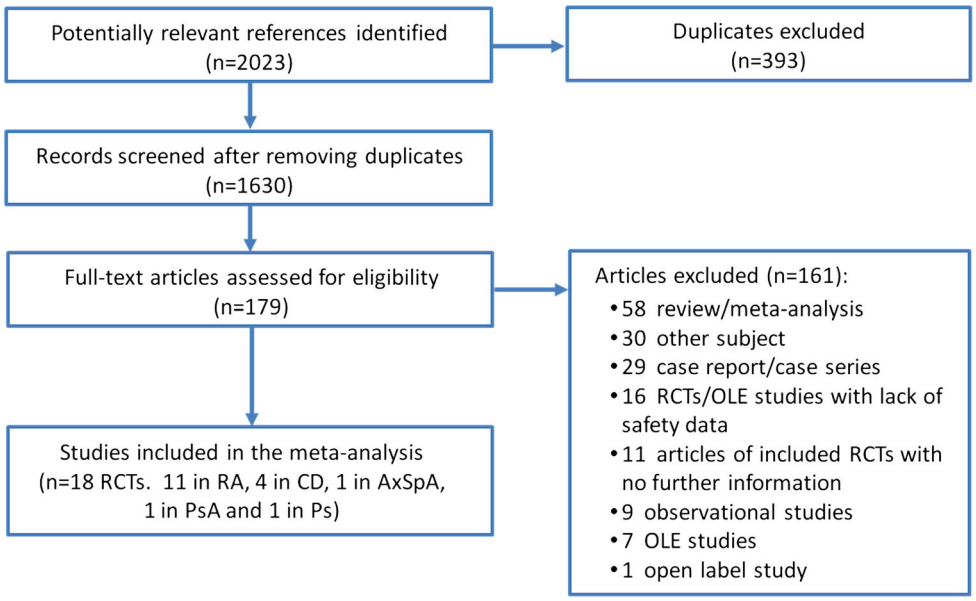


**Fig. 1** Flow diagram of the study selection process. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *OLE* open-label extension, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RCT* randomized controlled trial

and psoriasis (mean age 43.3 years) were younger than patients with RA (mean age 53.4 years) and PsA (mean age 47.5 years). CZP was administered every 2 or 4 weeks at 200 or 400 mg subcutaneously after loading doses of 200 or 400 mg at weeks 0, 2, and 4 (induction). Only the study by Schreiber et al. [6] and the J-RAPID (Japan RA Prevention of Structural Damage) trial [26] included a treatment arm with CZP 100 mg. In two studies all patients (including the placebo arm) received an induction treatment with CZP [19, 30] and 11 studies reported an induction phase where patients were randomized to receive CZP or placebo [20, 22–28, 31–33], whereas five studies did not comprise an induction phase [6, 17, 18, 21, 29].

Previous exposure to anti-TNF therapy was reported in 11 studies [6, 21, 22, 24–26, 28, 30–33]. In all studies conducted on CD patients, concomitant treatment could include immunomodulators, such as azathioprine, 6-mercaptopurine, methotrexate, or corticosteroids [6, 28–30]. Among the studies on RA, axSpA, and PsA patients, six studies used methotrexate as a scheduled treatment in combination with CZP or placebo [17, 19, 20, 22, 26, 27]. Moreover, comedications could include corticosteroids in eight studies [17, 18, 20–22, 24, 25, 32]; non-steroidal anti-inflammatory drugs in five studies [17, 18, 24, 25, 31]; and DMARDs in five studies [21, 23–25, 31], with the exception of methotrexate in the HIKARI study [25]. In the studies by Kang et al. [27] and Furst et al. [19], information on concomitant treatments were not reported. The only study including patients with psoriasis allowed prior use of anti-TNF drugs, but not methotrexate as concomitant treatment [33]. The study by Kivitz et al. [21] evaluated immune responses to pneumococcal and influenza vaccination in patients with RA treated with three doses of CZP 400 mg at weeks 0, 2, and 4.

The majority of studies indicated a treatment duration of 24 weeks [22, 23, 25–28, 30–32], three studies had a treatment duration ranging from 4 to 8 weeks [6, 21, 29], four studies had a treatment duration ranging from 12 to 20 weeks [17, 18, 24, 33], and in only two studies patients were treated for more than 24 weeks: 34 weeks in the DOSEFLEX study [19] and 52 weeks in the RAPID 1 study [20]. When considering the follow-up period, patients were observed for 24 weeks in six studies [23, 26, 27, 31–33], 6–12 weeks in four studies [6, 21, 24, 29], 26–36 weeks in seven studies [17–19, 22, 25, 28, 30], and up to 64 weeks in only one study [20]. A summary of the study characteristics is reported in Table 1.

### 3.3 Risk of Bias

The assessment of RCT quality disclosed a low overall risk of bias (Fig. 2). When considering selection bias (random sequence generation and allocation concealment), five studies [19–22, 27] were judged at unclear risk of bias owing to the lack of information; notably, for two studies [19, 27] only the abstract was available. Thirteen studies reported adequate methods of randomization and allocation concealment [6, 17, 18, 23–26, 28–33].

Performance bias was detected considering the blinding of participants and personnel. In particular, three studies [21, 23, 31] were considered at high risk of bias. The RAPID axSpA [31] and CERTAIN [CERTolizumab pegol in the treatment of RA: remission INduction and maintenance in patients with LDA (low disease activity)] [23] trials reported that CZP was administered by unblinded site personnel. The study by Kivitz and colleagues [21] was single-blind to patients. Eight studies were considered at low risk of performance bias [6, 17, 18, 25, 26, 30, 32, 33]. In seven studies [19, 20, 22, 24, 27–29] blinding of investigators was not clearly reported and they were scored as unclear for performance bias.

Detection bias was analyzed evaluating the blinding of outcome assessment. The only study at high risk of bias was that by Kivitz and colleagues [21], owing to the lack of investigator blinding. We rated 15 studies as at low risk of detection bias [6, 17, 18, 20, 22–26, 28–33]. Two studies were at unclear risk of bias because the information was not reported [19, 27].

With regard to attrition bias, seven studies were considered at high risk for incomplete outcome data, owing to the withdrawal rate of patients [17, 18, 22, 25, 26, 28, 33]. Six studies reported a considerable disproportion in the rate of withdrawals between the placebo group (range of withdrawal among studies 32–87 %) and treatment group (range of withdrawal among studies 7–31 %) [17, 18, 22, 25, 26, 33], mainly related to withdrawals due to lack of efficacy or disease progression in the control group. Otherwise, in the PRECiSE 1 (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1) study the rate of withdrawals was higher in the treatment group than control group (46 % of patients in the CZP 400 mg group vs. 39 % of patients in the placebo group) [28]. Nine studies were considered as at low risk of attrition bias [6, 20, 21, 23, 24, 28–31]. Notably, we scored the RAPID 1 study as being at low risk of attrition bias, despite it having a remarkable disproportion in the number of withdrawals between the control (78 %) and treatment (30–35 %) groups, because the authors described the exposure (patient-years) of patients to treatment (reporting the incidence for all safety outcomes) [20]. Two studies [19, 27] were judged as at unclear risk of bias owing to the lack of data about withdrawal rates in the article (only the abstract was available).

The risk of reporting bias was considered high in only two studies [19, 27] due to the lack of data concerning injection-site reactions [19] and neoplasms [19, 27]. All other studies displayed a low risk of reporting bias [6, 17, 18, 20–26, 28–33].

**Table 1** Main characteristics of the included studies

| References | Design | Study population | Treatment schedule | Drug and dose | No. of participants | Mean age [years (SD or range)] | Duration of treatment (weeks) | Follow-up (weeks) |
|---|---|---|---|---|---|---|---|---|
| Keystone et al. [20] | Phase III | RA | *Induction* (placebo + MTX or CZP 400 mg + MTX): weeks 0, 2, and 4<br>*Maintenance* (placebo + MTX or CZP 200 or 400 mg + MTX): q2w | Placebo + MTX | 199 | 52.2 (11.2) | 52 | 64 |
| | | | | CZP 200 mg + MTX | 393 | 51.4 (11.6) | | |
| | | | | CZP 400 mg + MTX | 390 | 52.4 (11.7) | | |
| Smolen et al. [22] | Phase III | RA | *Induction* (placebo + MTX or CZP 400 mg + MTX): weeks 0, 2, and 4<br>*Maintenance* (placebo + MTX or CZP 200 or 400 mg + MTX): q2w | Placebo + MTX | 127 | 51.5 (11.8) | 24 | 36 |
| | | | | CZP 200 mg + MTX | 246 | 52.2 (11.1) | | |
| | | | | CZP 400 mg + MTX | 246 | 51.9 (11.8) | | |
| Fleischmann et al. [18] | Phase III | RA | Placebo or CZP 400 mg: q4w | Placebo | 109 | 54.9 (11.6) | 20 | 32 |
| | | | | CZP 400 mg | 111 | 52.7 (12.7) | | |
| Weinblatt et al. [24] | Phase IIIb | RA | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4<br>*Maintenance* (placebo or CZP 200 mg): weeks 6, 8, and 10 | Placebo | 212 | 53.9 (12.7) | 12 | 12 |
| | | | | CZP 200 mg | 851 | 55.4 (12.4) | | |
| Choy et al. [17] | Phase III | RA | Placebo + MTX or CZP 400 mg + MTX: q4w | Placebo + MTX | 121 | 55.6 (11.7) | 20 | 32 |
| | | | | CZP 400 mg + MTX | 126 | 53.0 (12.3) | | |
| Yamamoto et al. [26] | Phase II/III | RA | *Induction* (placebo + MTX or CZP 200 or 400 mg + MTX): weeks 0, 2, and 4<br>*Maintenance* (placebo + MTX or CZP 100, 200, or 400 mg + MTX): q2w | Placebo + MTX | 77 | 51.9 (11.1) | 24 | 24 |
| | | | | CZP 100 mg + MTX | 72 | 54.3 (10.6) | | |
| | | | | CZP 200 mg + MTX | 82 | 50.6 (11.4) | | |
| | | | | CZP 400 mg + MTX | 85 | 55.4 (10.3) | | |
| Yamamoto et al. [25] | Phase III | RA | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4<br>*Maintenance* (placebo or CZP 200 mg): q2w | Placebo | 114 | 55.4 (9.8) | 24 | 36 |
| | | | | CZP 200 mg | 116 | 56.0 (10.2) | | |
| Kang et al. [27] | Phase III | RA | *Induction* (placebo + MTX or CZP 400 mg + MTX): weeks 0, 2, and 4<br>*Maintenance* (placebo + MTX or CZP 200 mg + MTX): q2w | Placebo + MTX | 40 | NA | 24 | 24 |
| | | | | CZP 200 mg + MTX | 81 | | | |
| Furst et al. [19] | Phase IIIb | RA | *Induction phase 1* (CZP 400 mg + MTX all patients): weeks 0, 2, and 4<br>*Induction phase 2* (CZP 200 mg + MTX all patients): q2w up to week 16<br>*Maintenance*: placebo + MTX or CZP 200 mg + MTX q2w or CZP 400 mg + MTX q4w | Placebo + MTX | 69 | NA | 34 | 34 |
| | | | | CZP 200 mg + MTX | 70 | | | |
| | | | | CZP 400 mg + MTX | 70 | | | |
| Smolen et al. [23] | Phase IIIb | RA | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4<br>*Maintenance* (placebo or CZP 200 mg): q2w | Placebo | 98 | 54.0 (12.4) | 24 | 24 |
| | | | | CZP 200 mg | 96 | 53.6 (11.9) | | |

**Table 1** continued

| References | Design | Study population | Treatment schedule | Drug and dose | No. of participants | Mean age [years (SD or range)] | Duration of treatment (weeks) | Follow-up (weeks) |
|---|---|---|---|---|---|---|---|---|
| Kivitz et al. [21] | Phase IV | RA | Placebo or CZP 400 mg: weeks 0, 2, and 4 | Placebo | 114 | 52.7 (11.1) | 4 | 6 |
| | | | (Influenza and pneumococcal vaccines: week 2) | CZP 400 mg | 110 | 53.1 (11.8) | | |
| Schreiber et al. [6] | Phase II | CD | Placebo or CZP 100, 200, or 400 mg: weeks 0, 4, and 8 | Placebo | 73 | 35.8 (19–64) | 8 | 12 |
| | | | | CZP 100 mg | 74 | 33.5 (18–56) | | |
| | | | | CZP 200 mg | 72 | 40.1 (19–71) | | |
| | | | | CZP 400 mg | 72 | 35.9 (18–67) | | |
| Sandborn et al. [28] | Phase III | CD | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4 | Placebo | 329 | 38 (18–77) | 24 | 26 |
| | | | | CZP 400 mg | 331 | 37 (18–73) | | |
| | | | *Maintenance* (placebo or CZP 400 mg): q4w | | | | | |
| Schreiber et al. [30] | Phase III | CD | *Induction* (CZP 400 mg all patients): weeks 0, 2, and 4 | Placebo | 212 | 38 (12) | 24 | 26 |
| | | | | CZP 400 mg | 216 | 38 (11) | | |
| | | | *Maintenance* (placebo or CZP 400 mg): q4w | | | | | |
| Sandborn et al. [29] | Phase III | CD | Placebo or CZP 400 mg: weeks 0, 2, and 4 | Placebo | 215 | 38.8 (12.8) | 4 | 6 |
| | | | | CZP 400 mg | 223 | 36.3 (12.6) | | |
| Landewé et al. [31] | Phase III | axSpA | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4 | Placebo | 107 | 39.9 (12.4) | 24 | 24 |
| | | | | CZP 200 mg | 111 | 39.1 (11.9) | | |
| | | | *Maintenance* (placebo or CZP 200 mg q2w or CZP 400 mg): q4w | CZP 400 mg | 107 | 39.8 (11.9) | | |
| Mease et al. [32] | Phase III | PsA | *Induction* (placebo or CZP 400 mg): weeks 0, 2, and 4 | Placebo | 136 | 47.3 (11.1) | 24 | 24 |
| | | | | CZP 200 mg | 138 | 48.2 (12.3) | | |
| | | | *Maintenance* (placebo or CZP 200 mg q2w or CZP 400 mg): q4w | CZP 400 mg | 135 | 47.1 (10.8) | | |
| Reich et al. [33] | Phase II | Ps | *Induction* (placebo or CZP 400 mg): week 0 | Placebo | 58 | 43.3 (12.8) | 12 | 24 |
| | | | *Maintenance* (placebo or CZP 200 or 400 mg): q2w | CZP 200 mg | 60 | 43.3 (10.1) | | |
| | | | | CZP 400 mg | 57 | 43.4 (11.7) | | |

*axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CZP* certolizumab pegol, *MTX* methotrexate, *NA* not available, *Ps* psoriasis, *PsA* psoriatic arthritis, *q2w* every 2 weeks, *q4w* every 4 weeks, *RA* rheumatoid arthritis, *SD* standard deviation

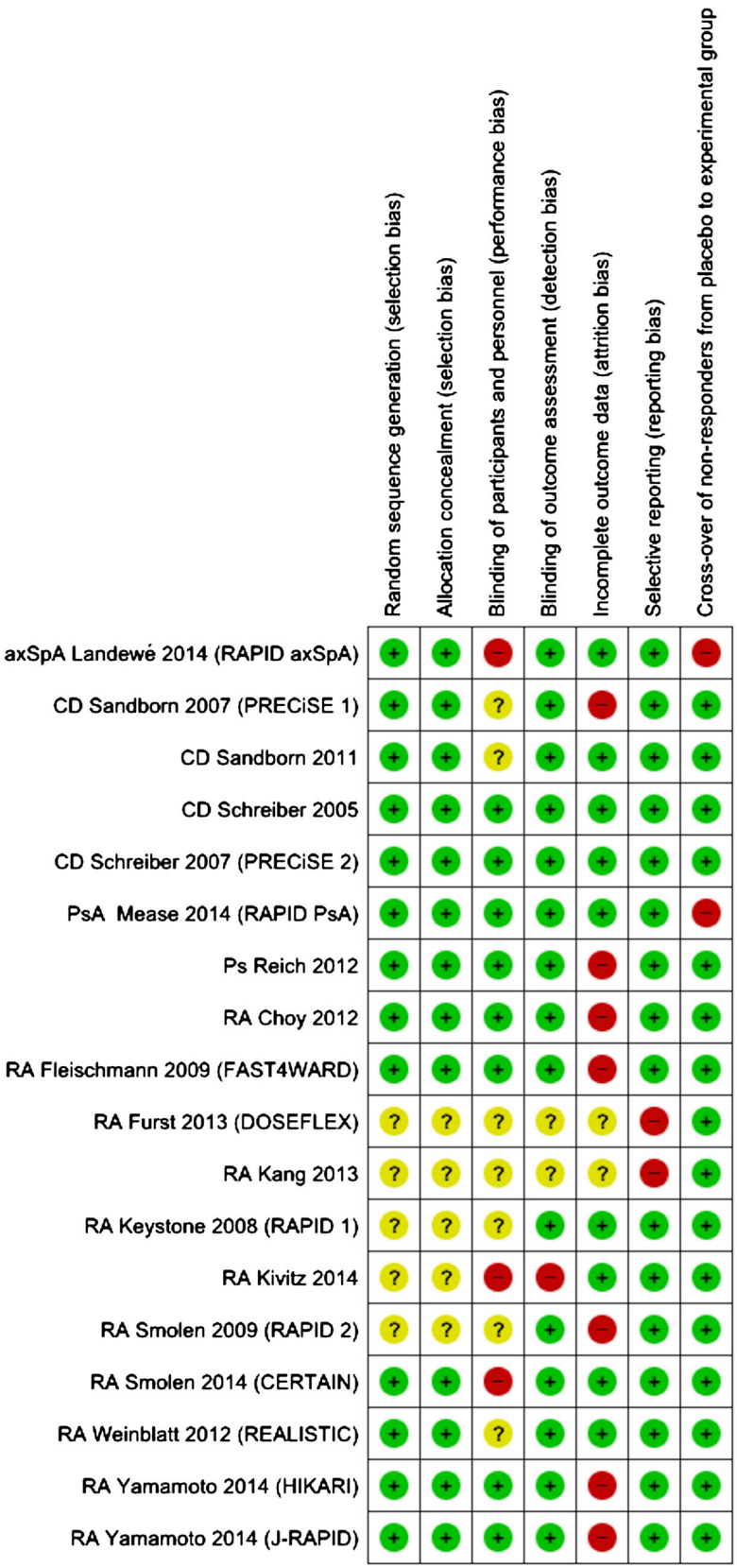


**Fig. 2** Risk of bias assessment of included studies. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

We considered the crossover of non-responders from placebo to the CZP group as another potential source of bias, since it might increase the number of AEs among placebo patients, thereby lowering the RRs for all safety outcomes. Two studies, RAPID axSpA [31] and RAPID PsA [32], were considered to be at high risk of bias since they allowed placebo escape to CZP groups for non-responder patients at week 16. These procedures could have underestimated AEs related to CZP treatment. Indeed, 16 studies displayed a low risk because the study design did not allow a crossover of non-responders to CZP [6, 17–30, 33].

### 3.4 Safety Outcomes

The overall RRs estimated for all safety outcomes are reported in Table 2, but some have not been addressed in this section. In the overall analysis, we did not find any significant heterogeneity among studies for the following safety outcomes: AEs; SAEs; withdrawals due to AEs; fatal AEs; infectious AEs; infectious SAEs; upper respiratory tract infections; neoplasms; and tuberculosis. By contrast, we detected a significant heterogeneity among studies for ADRs ($\chi^2 = 28.57$, $P = 0.005$; $I^2 = 58$ %; $\tau^2 = 0.04$) and injection-site reactions ($\chi^2 = 90.14$, $P < 0.00001$; $I^2 = 86$ %; $\tau^2 = 2.37$). Moreover, to assess the impact of CZP dosage, we separately reported the pooled RRs of all safety outcomes: for CZP 200 mg in Table 3 and CZP 400 mg in Table 4. Table 5 displays the RRs of all therapeutic indications according to CZP dosages (200 and 400 mg). Notably, this analysis included only one study for each of the following therapeutic indications: axSpA [31], PsA [32], and psoriasis [33]. The meta-regression analyses were only performed to explore the effect of CZP dosage on all safety outcomes, while the impact of diseases was not assessed because at least ten studies were available only for RA. The results of meta-regressions did not show a correlation between treatment with the highest CZP dosage (400 mg) and an increased risk of events for all safety outcomes, with the exception of injection-site reactions (coefficient 1.69; 95 % CI 0.13–3.25; $P = 0.036$). However, all of the between-study variance is not explained by the dosage, with an adjusted $R^2$ of 30.19 %, and a residual variance ($I^2$) due to a heterogeneity of 76.57 % ($\tau^2 = 1.64$).

#### *3.4.1 Adverse Events*

Among 18 studies [6, 17–33], 3157 patients in the CZP groups and 1531 patients in control groups experienced at least one AE during follow-up. The overall RR of AEs in CZP-treated versus control patients was 1.09 (95 % CI 1.04–1.14; $P = 0.0002$) (Fig. 3; Table 2). Tables 3 and 4 display the RRs of AEs for CZP 200 and 400 mg,

**Table 2** Overall risk ratios for all safety outcomes and their respective 95 % confidence intervals

| Safety outcome | Number of studies | Overall number of patients | Patients with events in CZP groups | Total patients in CZP groups | Patients with events in control groups | Total patients in control groups | Pooled risk ratios [95 % CI] |
|---|---|---|---|---|---|---|---|
| AEs | 18 | 6992 | 3157 | 4589 | 1531 | 2403 | 1.09 [1.04–1.14] |
| SAEs | 18 | 6992 | 360 | 4589 | 117 | 2403 | 1.50 [1.21–1.86] |
| ADRs | 13 | 5212 | 1083 | 3294 | 508 | 1918 | 1.20 [1.03–1.39] |
| Withdrawals due to AEs | 16 | 6662 | 235 | 4368 | 121 | 2294 | 1.14 [0.89–1.45] |
| Fatal AEs | 16 | 6345 | 16 | 4226 | 1 | 2119 | 2.04 [0.69–6.04] |
| Infectious AEs | 14 | 6218 | 1247 | 4147 | 415 | 2071 | 1.28 [1.13–1.45] |
| Infectious SAEs | 18 | 6992 | 125 | 4589 | 21 | 2403 | 2.17 [1.36–3.47] |
| Upper respiratory tract infections | 14 | 6004 | 509 | 4034 | 199 | 1970 | 1.34 [1.15–1.57] |
| Injection-site reactions | 14 | 6224 | 196 | 4105 | 145 | 2119 | 1.59 [0.63–3.99] |
| Neoplasms | 16 | 6662 | 25 | 4369 | 9 | 2294 | 1.04 [0.49–2.22] |
| Tuberculosis | 18 | 6992 | 14 | 4589 | 0 | 2403 | 2.47 [0.64–9.56] |

*ADRs* adverse drug reactions, *AEs* adverse events, *CI* confidence interval, *CZP* certolizumab pegol, *SAEs* serious adverse events

**Table 3** Risk ratios of certolizumab pegol 200 mg for all safety outcomes and their respective 95 % confidence intervals

| Safety outcome | Number of studies | Total patients | Patients with events in CZP 200 mg groups | Total patients in CZP 200 mg groups | Patients with events in control groups | Total patients in control groups | Pooled risk ratios [95 % CI] for CZP 200 mg |
|---|---|---|---|---|---|---|---|
| AEs | 12 | 3617 | 1589 | 2312 | 811 | 1305 | 1.12 [1.07–1.18] |
| SAEs | 12 | 3617 | 174 | 2312 | 56 | 1305 | 1.62 [1.16–2.26] |
| ADRs | 8 | 2184 | 463 | 1255 | 243 | 929 | 1.43 [1.25–1.62] |
| Withdrawals due to AEs | 10 | 3357 | 102 | 2161 | 38 | 1196 | 1.45 [0.99–2.14] |
| Fatal AEs | 11 | 3478 | 8 | 2242 | 1 | 1236 | 1.82 [0.50–6.63] |
| Infectious AEs | 10 | 3357 | 708 | 2161 | 321 | 1196 | 1.23 [1.05–1.44] |
| Infectious SAEs | 12 | 3617 | 71 | 2312 | 10 | 1305 | 2.64 [1.44–4.84] |
| Upper respiratory tract infections | 10 | 3357 | 301 | 2161 | 144 | 1196 | 1.33 [1.05–1.70] |
| Injection-site reactions | 8 | 3004 | 105 | 1983 | 8 | 1021 | 4.66 [2.35–9.24] |
| Neoplasms | 10 | 3357 | 13 | 2161 | 7 | 1196 | 0.81 [0.30–2.17] |
| Tuberculosis | 12 | 3617 | 7 | 2312 | 0 | 1305 | 2.83 [0.50–16.01] |

*ADRs* adverse drug reactions, *AEs* adverse events, *CI* confidence interval, *CZP* certolizumab pegol, *SAEs* serious adverse events

**Table 4** Risk ratios of certolizumab pegol 400 mg for all safety outcomes and their respective 95 % confidence intervals

| Safety outcome | Number of studies | Total patients | Patients with events in CZP 400 mg groups | Total patients in CZP 400 mg groups | Patients with events in control groups | Total patients in control groups | Pooled risk ratios [95 % CI] for CZP 400 mg |
|---|---|---|---|---|---|---|---|
| AEs | 14 | 4219 | 1568 | 2277 | 1246 | 1942 | 1.08 [1.02–1.15] |
| SAEs | 14 | 4219 | 186 | 2277 | 95 | 1942 | 1.58 [1.23–2.02] |
| ADRs | 11 | 3745 | 620 | 2039 | 458 | 1706 | 1.13 [0.95–1.35] |
| Withdrawals due to AEs | 13 | 4080 | 133 | 2207 | 104 | 1873 | 1.19 [0.86–1.64] |
| Fatal AEs | 12 | 3642 | 8 | 1984 | 1 | 1658 | 2.37 [0.65–8.59] |
| Infectious AEs | 11 | 3636 | 539 | 1986 | 305 | 1650 | 1.33 [1.12–1.58] |
| Infectious SAEs | 14 | 4219 | 54 | 2277 | 15 | 1942 | 2.32 [1.27–4.24] |
| Upper respiratory tract infections | 11 | 3422 | 208 | 1873 | 136 | 1549 | 1.40 [1.14–1.71] |
| Injection-site reactions | 12 | 3918 | 91 | 2122 | 143 | 1796 | 1.12 [0.44–2.86] |
| Neoplasms | 13 | 4080 | 12 | 2207 | 4 | 1873 | 1.74 [0.64–4.72] |
| Tuberculosis | 14 | 4219 | 7 | 2277 | 0 | 1942 | 3.02 [0.65–14.12] |

*ADRs* adverse drug reactions, *AEs* adverse events, *CI* confidence interval, *CZP* certolizumab pegol, *SAEs* serious adverse events

respectively. Based on ten studies [17–19, 21–27] in RA patients and four studies [6, 28–30] in patients with CD, there were no differences in the number of AEs between patients treated with CZP 200 and 400 mg (Table 5).

### 3.4.2 Serious Adverse Events

All of the included studies provided information about the occurrence of SAEs (360 patients in the CZP groups and 117 patients in the control groups) [6, 17–33]. The overall RR was 1.50 (95 % CI 1.21–1.86; $P = 0.0002$) (Fig. 4; Table 2). Tables 3 and 4 show the RRs of SAEs for CZP 200 and 400 mg. In patients with RA (11 studies) [17–27] the RR was higher than the overall estimation for either the CZP 200 mg (RR 1.88; 95 % CI 1.14–3.09; $P = 0.01$) or CZP 400 mg (RR 1.98; 95 % CI 1.34–2.93; $P = 0.0006$) group (Table 5). In CD patients (four studies) [6, 28–30] the RR for the CZP 200 mg groups (RR 1.69; 95 % CI 0.65–4.41; $P = 0.28$) was slightly higher than the overall RR, while in the CZP 400 mg groups (RR 1.24; 95 % CI 0.87–1.77; $P = 0.24$) the RR was lower (Table 5). The RRs of all other therapeutic indications are displayed in Table 5.

### 3.4.3 Infectious Adverse Events and Infectious Serious Adverse Events

In 14 studies [6, 17, 20, 22–26, 28–33], infectious AEs affected 1247 CZP patients and 415 control patients, yielding an overall RR of 1.28 (95 % CI 1.13–1.45; $P = 0.0002$) (Table 2). Notably, five studies [21, 26, 28, 30, 33] reported that infectious AEs occurred in ≥5 % of patients in each study group, while one study [25] reported that infectious AEs occurred in ≥3 % of patients in each study group. Infectious AEs occurred mainly in the respiratory tract (pharyngitis, naso-pharyngitis, sinusitis, flu-like symptoms), urinary tract, and gastrointestinal district (gastroenteritis and perianal abscesses). In particular, upper respiratory tract infections occurred in 509 and 199 patients in the CZP and control groups (14 studies) [6, 17, 20–26, 28, 30–33], respectively, with an RR of 1.34 (95 % CI 1.15–1.57; $P = 0.0002$) (Table 2).

With regard to infectious SAEs in 18 studies [6, 17–33], they occurred in 125 and 21 patients randomized to the CZP and control groups, respectively. The overall RR was 2.17 (95 % CI 1.36–3.47; $P = 0.001$) (Fig. 5; Table 2). Respiratory tract infections were the most frequently reported infectious SAEs, followed by infections of the urinary tract and gastrointestinal tract. Tables 3 and 4 show the RR of infectious SAEs for CZP 200 and 400 mg. In RA patients (11 studies) [17–27], the RR of infectious SAEs was higher than the overall estimation for both CZP 200 mg (RR 2.86; 95 % CI 1.46–5.57; $P = 0.002$) and 400 mg (RR 3.80; 95 % CI 1.42–10.14; $P = 0.008$) (Table 5). In CD patients (four studies) [6, 28–30], the RR of infectious SAEs was lower for both CZP 200 mg (RR 0.34; 95 % CI 0.01–8.16; $P = 0.50$) and 400 mg (RR 1.56; 95 % CI 0.68–3.60; $P = 0.30$) (Table 5). The RRs of other therapeutic indications are displayed in Table 5.

### 3.4.4 Injection-Site Reactions

Fourteen studies [6, 17, 18, 20–22, 24, 25, 28–33] reported injection-site reactions, with an overall RR of 1.59 (95 % CI 0.63–3.99; $P = 0.33$) (Fig. 6; Table 2). Of note, the J-RAPID study, which evaluated the efficacy and safety of three dosages of CZP (100, 200, and 400 mg) in patients with RA, was excluded because the number of patients with injection-site reactions was reported as the total number of cases for all CZP treatment groups, including patients treated with CZP 100 mg [26]. Tables 3 and 4 display the RRs of injection-site reactions for CZP 200 and 400 mg. Table 5 shows the RRs of injection-site reactions for all therapeutic indications according to dosage.

### 3.4.5 Neoplasms

Based on 16 studies [6, 17, 18, 20–26, 28–33], 25 CZP patients and nine control patients developed neoplasms. The overall RR was 1.04 (95 % CI 0.49–2.22; $P = 0.92$) (Table 2). The RR of neoplasms in CZP-treated patients was 0.81 (95 % CI 0.30–2.17; $P = 0.67$) for CZP 200 mg patients (Table 3) and 1.74 (95 % CI 0.64–4.72; $P = 0.28$) for CZP 400 mg patients (Table 4). In RA patients (nine studies) [17, 18, 20–26], the RR was 0.70 (95 % CI 0.25–1.98; $P = 0.50$) and 1.88 (95 % CI 0.49–7.27; $P = 0.36$) for CZP 200 and 400 mg, respectively (Table 5). Among CD patients (four studies) [6, 28–30], the RR was 3.04 (95 % CI 0.13–73.44; $P = 0.49$) in CZP 200 mg patients and 1.33 (95 % CI 0.25–7.04; $P = 0.74$) in CZP 400 mg patients (Table 5). The RRs of neoplasms for all other indications are detailed in Table 5.

### 3.4.6 Tuberculosis

Tuberculosis occurred in 14 CZP-treated patients from 18 studies [6, 17–33]. No tuberculosis cases were recorded in control groups. The overall RR estimate was 2.47 (95 % CI 0.64–9.56; $P = 0.19$) (Table 2). When considering the dosages of CZP separately, in the CZP 200 mg groups cases of tuberculosis were recorded only in RA patients (seven cases) and the RR was 2.83 (95 % CI 0.50–16.01; $P = 0.24$) (Table 3); in the CZP 400 mg groups the RR was 3.02 (95 % CI 0.65–14.12; $P = 0.16$) based on five cases in RA patients, and one case among either CD and psoriasis patients (Table 4). The RRs of tuberculosis for

**Table 5** Risk ratios for all safety outcomes and their respective 95 % confidence intervals, stratified on the basis of disease and certolizumab pegol dosage

| Safety outcome | CZP 200 mg (RR [95 % CI]) | CZP 400 mg (RR [95 % CI]) |
|---|---|---|
| Rheumatoid arthritis | | |
| AEs | 1.14 [1.07–1.21] | 1.13 [1.03–1.25] |
| SAEs | 1.88 [1.14–3.09] | 1.98 [1.34–2.93] |
| ADRs | 1.49 [1.26–1.77] | 1.29 [1.03–1.62] |
| Withdrawals due to AEs | 1.66 [1.05–2.63] | 2.16 [1.22–3.85] |
| Fatal AEs | 1.66 [0.40–6.80] | 2.11 [0.44–10.14] |
| Infectious AEs | 1.29 [1.08–1.52] | 1.44 [1.04–1.99] |
| Infectious SAEs | 2.86 [1.46–5.57] | 3.80 [1.42–10.14] |
| Upper respiratory tract infections | 1.34 [1.05–1.71] | 1.38 [0.96–1.97] |
| Injection-site reactions | 7.76 [2.66–22.63] | 0.77 [0.20–2.89] |
| Neoplasms | 0.70 [0.25–1.98] | 1.88 [0.49–7.27] |
| Tuberculosis | 2.83 [0.50–16.01] | 3.04 [0.37–25.22] |
| Crohn's disease | | |
| AEs | 1.09 [0.90–1.33] | 1.01 [0.96–1.08] |
| SAEs | 1.69 [0.65–4.41] | 1.24 [0.87–1.77] |
| ADRs | 1.36 [1.04–1.77] | 0.91 [0.76–1.10] |
| Withdrawals due to AEs | 1.01 [0.37–2.74] | 0.85 [0.63–1.16] |
| Fatal AEs | NE | 2.98 [0.12–72.93] |
| Infectious AEs | 1.31 [0.76–2.26] | 1.30 [0.94–1.79] |
| Infectious SAEs | 0.34 [0.01–8.16] | 1.56 [0.68–3.60] |
| Upper respiratory tract infections | 1.32 [0.62–2.81] | 1.33 [0.84–2.10] |
| Injection-site reactions | 2.03 [0.38–10.73] | 0.64 [0.12–3.43] |
| Neoplasms | 3.04 [0.13–73.44] | 1.33 [0.25–7.04] |
| Tuberculosis | NE | 2.94 [0.12–71.88] |
| Axial spondyloarthritis | | |
| AEs | 1.22 [1.02–1.46] | 1.19 [0.99–1.43] |
| SAEs | 0.77 [0.21–2.80] | 1.40 [0.46–4.27] |
| ADRs | 1.80 [1.15–2.80] | 1.64 [1.04–2.59] |
| Withdrawals due to AEs | 0.96 [0.14–6.72] | 2.00 [0.37–10.69] |
| Fatal AEs | NE | NE |
| Infectious AEs | 1.66 [1.09–2.51] | 1.64 [1.08–2.49] |
| Infectious SAEs | 4.82 [0.23–99.28] | NE |
| Upper respiratory tract infections | 1.64 [0.79–3.42] | 1.50 [0.71–3.19] |
| Injection-site reactions | 9.64 [1.26–74.02] | 5.00 [0.59–42.08] |
| Neoplasms | NE | NE |
| Tuberculosis | NE | NE |
| Psoriatic arthritis | | |
| AEs | 1.01 [0.86–1.19] | 1.05 [0.90–1.23] |
| SAEs | 1.31 [0.47–3.69] | 2.18 [0.85–5.57] |
| ADRs | 1.04 [0.71–1.52] | 1.12 [0.77–1.62] |
| Withdrawals due to AEs | 1.97 [0.37–10.58] | 3.02 [0.62–14.71] |
| Fatal AEs | 2.96 [0.12–71.95] | 3.02 [0.12–73.53] |
| Infectious AEs | 1.14 [0.85–1.51] | 1.05 [0.78–1.41] |
| Infectious SAEs | 1.97 [0.18–21.48] | 2.01 [0.18–21.96] |
| Upper respiratory tract infections | 1.78 [1.11–2.87] | 1.82 [1.13–2.94] |
| Injection-site reactions | 1.97 [0.50–7.72] | 4.37 [1.27–14.97] |
| Neoplasms | NE | 3.02 [0.12–73.53] |
| Tuberculosis | NE | NE |

**Table 5** continued

| Safety outcome | CZP 200 mg (RR [95 % CI]) | CZP 400 mg (RR [95 % CI]) |
|---|---|---|
| Psoriasis | | |
| AEs | 1.01 [0.81–1.28] | 0.99 [0.78–1.26] |
| SAEs | 1.93 [0.18–20.75] | 3.05 [0.33–28.49] |
| ADRs | – | – |
| Withdrawals due to AEs | 0.64 [0.11–3.72] | 0.68 [0.12–3.91] |
| Fatal AEs | NE | NE |
| Infectious AEs | 0.64 [0.38–1.08] | 1.14 [0.76–1.73] |
| Infectious SAEs | 2.90 [0.12–69.81] | 5.09 [0.25–103.67] |
| Upper respiratory tract infections | 0.51 [0.25–1.05] | 0.96 [0.54–1.70] |
| Injection-site reactions | 14.51 [0.85–248.38] | 7.12 [0.38–134.82] |
| Neoplasms | NE | NE |
| Tuberculosis | NE | 3.05 [0.13–73.39] |

*ADRs* adverse drug reactions, *AEs* adverse events, *CI* confidence interval, *CZP* certolizumab pegol, *NE* not estimable (no cases in each group), *RR* risk ratio, *SAEs* serious adverse events

therapeutic indications among CZP 200 and 400 mg are described in Table 5.

## 4 Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis evaluating the overall safety profile of CZP in patients with IMIDs. We pooled results from 18 studies (11 in RA patients, four in CD, and one each in axSpA, PsA, and psoriasis patients), covering a total of 6992 patients followed for up to 52 weeks to estimate the risk of AEs, SAEs, ADRs, withdrawals due to AEs, fatal AEs, infectious AEs and SAEs, upper respiratory tract infections, injection-site reactions, neoplasms, and tuberculosis. Our analysis highlighted an overall favorable safety profile of CZP across all therapeutic indications, even though we found a significant risk of AEs, ADRs, infectious AEs and SAEs, and upper respiratory tract infections associated with CZP. Of note, the above risks are mainly related to RA, while in patients with CD we found a significant risk only for ADRs in the 200 mg group. When considering the other therapeutic indications, we observed a significant risk of AEs in patients with axSpA treated with CZP 200 mg, as well as injection-site reactions in patients with axSpA and PsA treated with CZP 200 and 400 mg, respectively. Nevertheless, the estimated risks in patients with axSpA, PsA, and psoriasis cannot be generalized to their respective patient populations since only one RCT was carried out for each of these therapeutic indications. With regard to the effect of CZP dosage, the present findings do not show any significant difference between 200 and 400 mg, but the risk of injection-site reactions was significantly higher for CZP 200 mg than for the CZP 400 mg group. This difference can be explained by the circumstance that, among the authors who tested CZP at the dose of 400 mg, Choy et al. [17] and Fleischmann et al. [18] used a solution containing sorbitol as placebo, which likely increased the rate of cases of injection-site reactions in control groups, thus reducing the RR values in the CZP 400 mg groups. Another important finding of our analysis indicates that the risk of infectious SAEs associated with CZP was more than twofold higher than control groups, an outcome that could have contributed to higher discontinuation rates, particularly in RA patients.

When considering therapeutic indications, the overall risk of infectious SAEs was considerably driven by RA. It is well-known that RA patients are at higher risk of infections, owing to the pathophysiology of the disease and to concomitant treatments with traditional DMARDs, such as methotrexate, leflunomide, chloroquine, and corticosteroids [34]. Moreover, RA patients in our meta-analysis were older than patients with other IMIDs, particularly as compared to CD patients (53.4 vs. 37.5 years), a condition that could justify an increased risk of infections. In RA patients, respiratory tract infections were the most frequently reported infectious SAEs, including 12 of 14 cases of tuberculosis, followed by infections of the urinary and gastrointestinal tract. Moreover, we observed a significant risk of infectious AEs in patients with RA. With regard to the risk of neoplasms, we found only a trend toward a higher frequency of cases among CZP patients, particularly in RA, than in control groups.

Upon comparison of the safety profile of CZP with other anti-TNF agents, CZP seems to be associated with a higher occurrence of serious infections. Indeed, in the meta-analysis by Singh and co-workers [35], the odds ratio (OR) of serious infections was significantly higher for CZP (OR

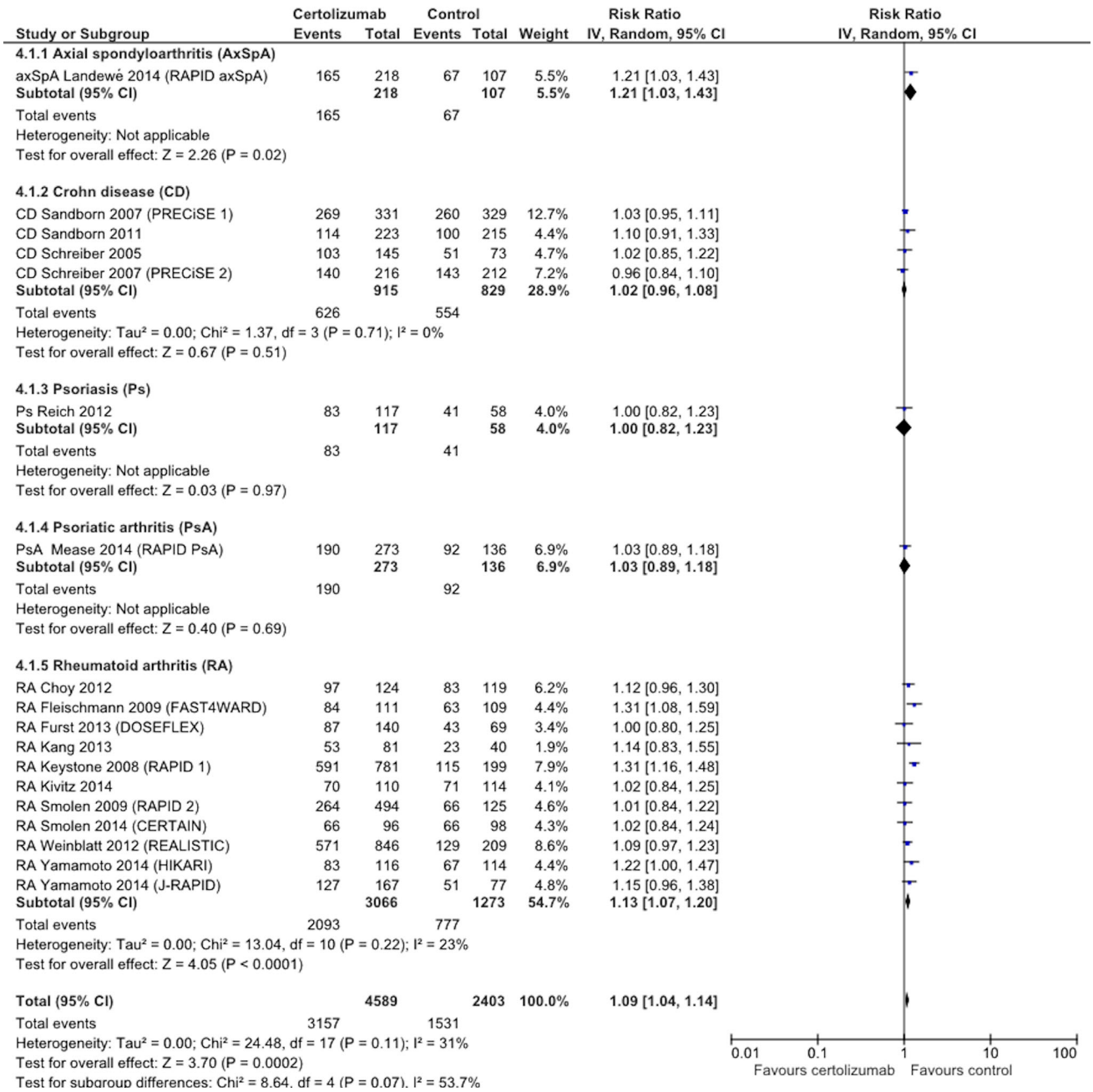


**Fig. 3** Risk ratios of adverse events and their respective 95 % confidence intervals, overall and by disease. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

3.51, 95 % CI 1.59–7.79), while it was not significant for all other anti-TNF agents (adalimumab, OR 1.12, 95 % CI 0.73–1.70; golimumab, OR 1.29, 95 % CI 0.71–2.35; etanercept, OR 1.06, 95 % CI 0.74–1.51; infliximab, OR 1.45, 95 % CI 0.99–2.13) [35]. When considering the risk of malignancies, our analysis did not show any significant risk, which is similar to other anti-TNF drugs. The meta-analysis by Lopez-Olivo et al. [36] estimated the risk of malignancies in RA patients treated with anti-TNF drugs associated with methotrexate or other DMARDs. Individually, none of the TNF inhibitors displayed a significant risk. In particular, the Peto OR for CZP was 1.5 (95 % CI 0.44–4.9), as compared with adalimumab 1.6 (95 % CI 0.61–4.3), etanercept 1.3 (95 % CI 0.50–3.4), golimumab 0.83 (95 % CI 0.30–2.4), or infliximab 1.7 (95 % CI 0.80–3.4). Moreover, no differences were highlighted when TNF inhibitors alone were compared with controls (methotrexate or DMARDs alone) [36]. The same trend

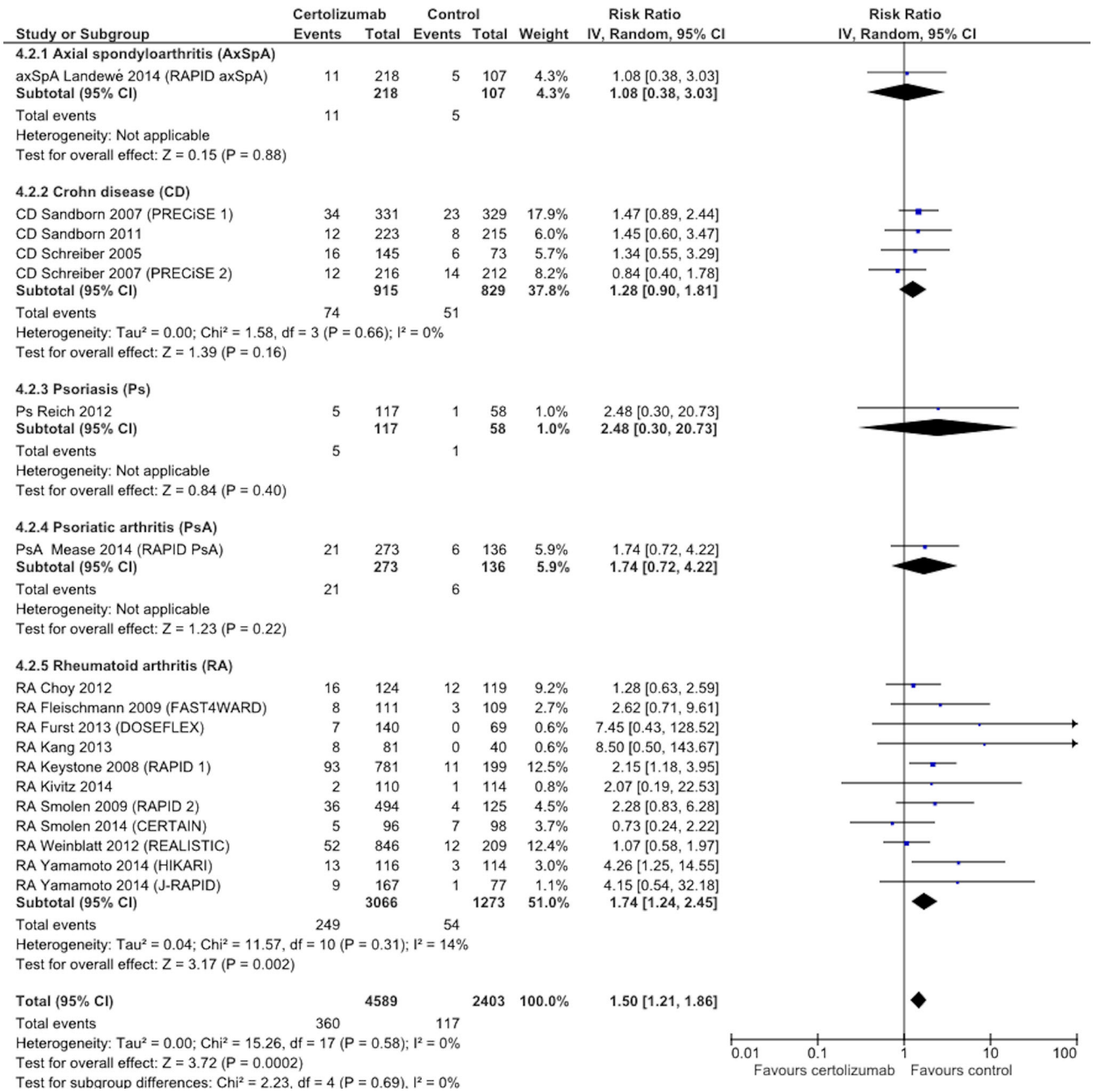


**Fig. 4** Risk ratios of serious adverse events and their respective 95 % confidence intervals, overall and by disease. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

was observed in CD patients, since Williams et al. [37] did not find any significant RR of malignancies for all anti-TNF drugs (adalimumab, RR 0.46, 95 % CI 0.11–1.92; golimumab, RR: 1.52, 95 % CI 0.16–14.49; infliximab, RR 0.70, 95 % CI 0.23–2.15) [37].

The biologic mechanism underlying the higher risk of infections with anti-TNF agents can be explained considering the role of TNF in the host response against pathogens. TNF is a pleiotropic cytokine involved in the control of a wide variety of biologic functions, including inflammatory reactions, immune responses, and neoplastic cell transformation [38]. At physiologic concentrations, TNF can exert beneficial effects, enhancing the host defense mechanisms against infections and promoting pro-apoptotic pathways in tumor cells. At higher concentrations, TNF can lead to excess inflammation and organ injury [38]. Indeed, under pathological conditions, long-term exposure of tissues to TNF can suppress adaptive immunity and

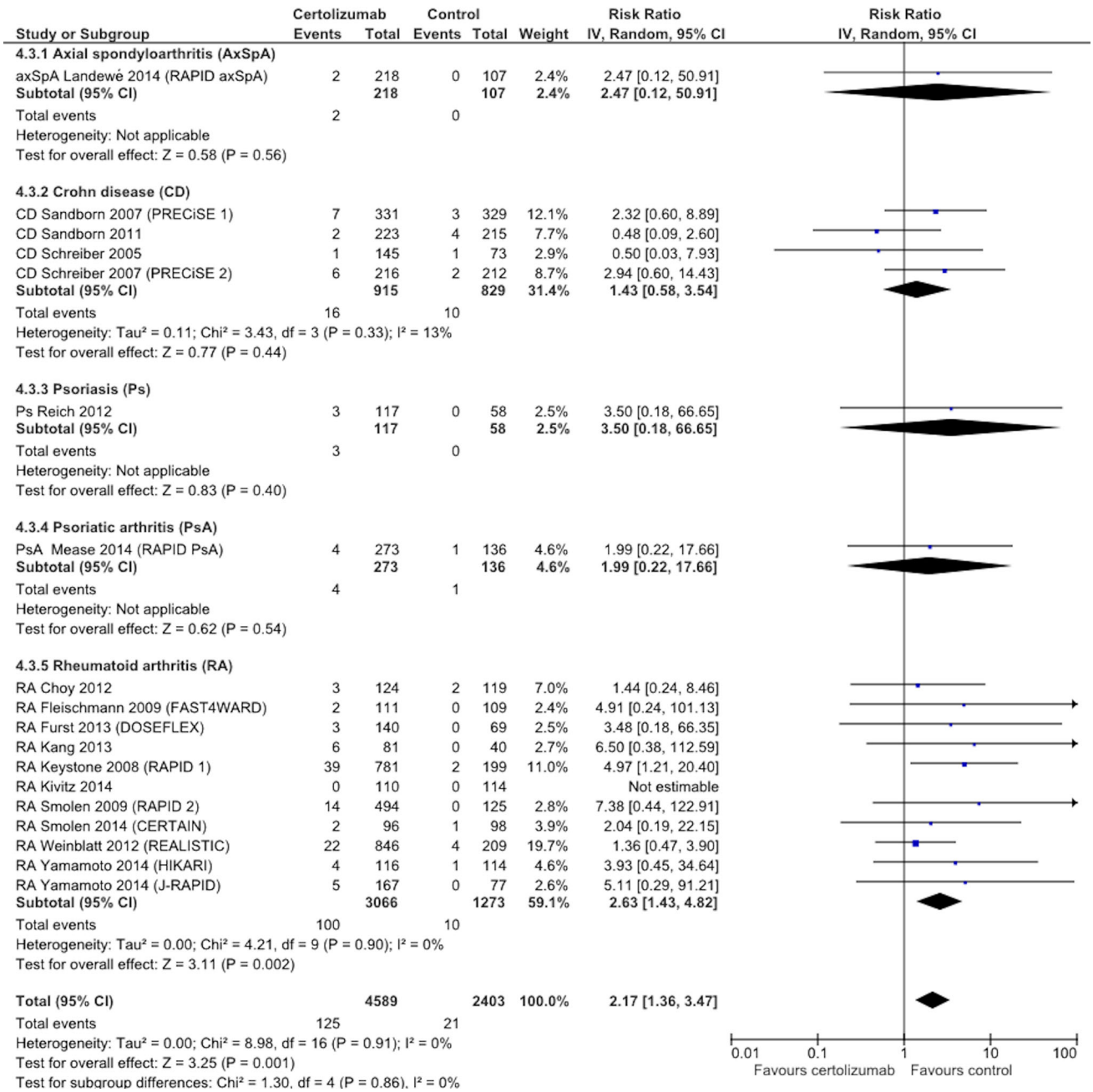


**Fig. 5** Risk ratios of infectious serious adverse events and their respective 95 % confidence intervals, overall and by disease. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

T cell functions, thus playing a critical role in the pathogenesis of IMIDs, such as RA, CD, axSpA, PsA, and psoriasis [39]. On this basis, the removal of excess TNF from sites of inflammation has been validated as a viable therapeutic strategy for the management of several IMIDs [39]. However, at the same time, it is expected that considerable reductions of TNF levels, associated with the administration of anti-TNF agents, can lead to increased incidence of infections. In support of this contention, safety data provided by RCTs and observational studies based on registers showed an increased risk of infectious adverse effects, with particular regard for tuberculosis and other infections caused by intracellular microorganisms, following treatment with anti-TNF agents [40, 41].

Another issue pertaining to the safety profile of anti-TNF agents is related to their antibody structure. Infliximab, adalimumab, and golimumab are full monoclonal antibodies equipped with a full Fc region, etanercept is a

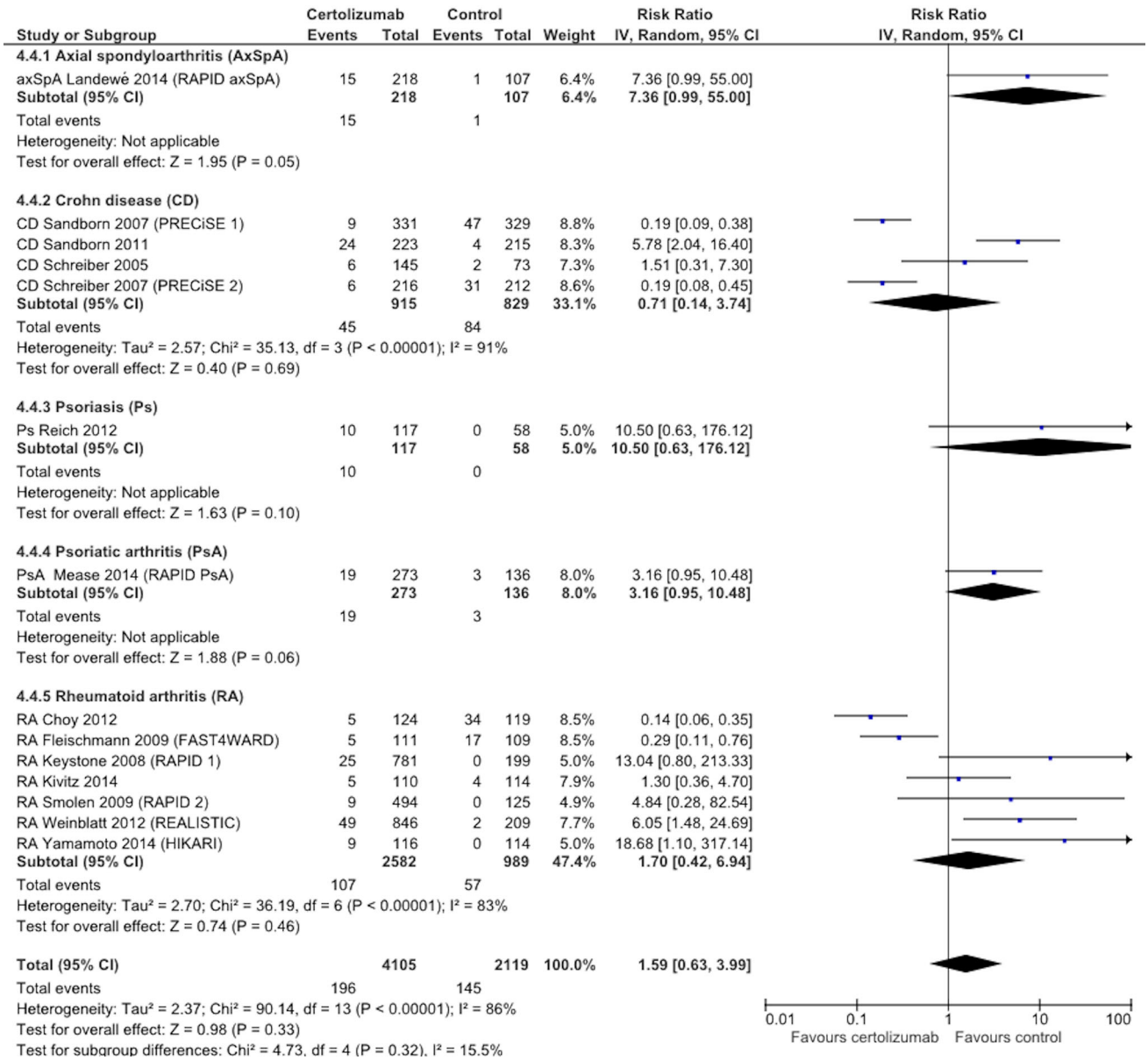


**Fig. 6** Risk ratios of injection-site reactions and their respective 95 % confidence intervals, overall and by disease. *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

fusion protein of two TNF soluble receptors linked to a Fc human fragment, while CZP is a single Fab' fragment of a humanized monoclonal antibody conjugated with a 40 kDa PEG moiety (91 kDa). Of note, full monoclonal antibodies can exert all Fc-dependent effects, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), while etanercept, despite having an Fc region, lacks the $C_H1$ domains of both Fab' regions and therefore displays an impaired CDC activity. CZP does not exert CDC and ADCC activities as it lacks the Fc region. Differences in the antibody structure also account for different patterns of TNF binding by anti-TNF drugs. In particular, anti-TNF agents endowed with full antibody structure can form multimeric complexes with transmembrane TNF, leading to suppression of T cell proliferation, decrease in cytokine production, and induction of apoptosis via activation of reverse signaling [38].

Since CDC, ADCC, and apoptosis are currently regarded as the most prominent mechanisms through which anti-TNF drugs can destabilize granulomas and promote the reactivation of tuberculosis infections [42, 43], anti-TNF agents endowed with full antibody structure are expected to

be associated with a higher risk of tuberculosis. In line with this expectation, in the clinical setting the risk of tuberculosis reactivation was found to be higher with infliximab and adalimumab than etanercept, particularly in RA patients [42, 43]. By contrast, however, CZP displayed a similar risk of tuberculosis reactivation as that of fully antibody agents [44], thus implying that other, yet unknown, mechanisms than CDC, ADCC, and reverse signaling are likely to contribute to the reactivation of tuberculosis infection. It is also noteworthy that different IMIDs hold a different risk of tuberculosis reactivation. Indeed, patients with inflammatory bowel diseases (such as CD) display a substantially lower risk of tuberculosis reactivation than those with RA [45], and, in the present analysis, only one case of tuberculosis infection was found among CD patients, while the majority of cases occurred in the RA groups (12 of 14 cases).

Our meta-analysis has some limitations. First, some studies [21, 25, 26, 28, 30, 33] reported the frequency of infectious AEs only for events that occurred in more than 3–5 % of patients, likely resulting in an underestimation of infectious AE rates. Second, switch of non-responders from placebo to CZP groups could have biased the estimation of AEs risk, since in the intention-to-treat analysis the events occurring in patients switched from placebo to CZP were ascribed to placebo, with a consequent underestimation of RR values [31, 32]. Third, the higher rate of withdrawals in the control groups in one-third of the studies than in the CZP groups could have decreased the rate of AEs in the control group, thus leading to a higher estimation of RRs for all safety outcomes [17, 18, 22, 25, 26, 33]. Lastly, the relatively small number of included studies and duration of follow-up (mainly less than 1 year) could have prevented us from achieving significance for risk of rare AEs, such as malignancies and tuberculosis. However, despite the above limitations, our findings are strengthened by the circumstance that the majority of included studies were of high quality, and there was no significant heterogeneity among the studies for most of the safety outcomes.

## 5 Conclusions

Current data on the safety of CZP suggest an overall favorable tolerability profile, with the exception of serious infections, which appear to occur mainly in RA patients, who have a more than twofold higher risk than controls. Notably, these conclusions are supported by pre-authorization trials. Therefore, large observational studies with long-term exposure to CZP or the analysis of data from national registries of ADRs are required to improve our knowledge on the safety profile of CZP, particularly for rare AEs that might occur following long-term exposures. In the meantime, spontaneous reporting of suspected adverse reactions to CZP is highly recommended.

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**Compliance with Ethical Standards**

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