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PSORIASIS (J WU, SECTION EDITOR)

Certolizumab Pegol for Psoriasis and Psoriatic Arthritis

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Abstract

Purpose of Review The purpose of this review is to provide an overview of the use of certolizumab pegol (Cimzia®, UCB S.A.) for psoriasis and psoriatic arthritis and summarize important findings.

Recent Findings Three pivotal phase three clinical trials CIMPASI-1, CIMPASI-2, and CIMPACT have demonstrated efficacy and safety of certolizumab pegol (CZP) in patients with plaque psoriasis. In addition, another multicenter phase three clinical trial, RAPID-PsA, has shown long-term efficacy and safety data of CZP in psoriatic arthritis.

Summary When compared with other TNF-alpha blockers, CZP has demonstrated increased efficacy in psoriasis. In addition, CZP has also shown clinically significant and sustained improvement in psoriatic arthritis based on symptoms and radiographic evidence in patients with up to 4 years of follow-up. The safety profile of CZP is comparable to other anti-TNF agents. Finally, CZP's unique structure as a PEGylated monoclonal antibody fragment prevents placental transfer and therefore may make it an ideal choice as a biologic medication for women of childbearing age.

Keywords Psoriasis · Certolizumab pegol · Psoriatic arthritis · Biologic · Efficacy · Safety

Introduction

The use of biologic agents for the treatment of psoriasis has increased significantly within the last decade. Tumor necrosis factor alpha (TNF-alpha) has long been implicated as a key mediator of multiple proinflammatory pathways in psoriasis [1]. Certolizumab pegol (CZP) is a PEGylated monoclonal antibody directed against TNF-alpha. Currently, CZP is FDA approved for treatment in adults for the following six conditions: moderate-to-severe psoriasis in candidates for systemic therapy or phototherapy, active psoriatic arthritis, moderately to severely active rheumatoid arthritis, active ankylosing spondylitis, moderately to severely active Crohn's disease that has had inadequate response to conventional therapy, and active non-radiographic axial spondyloarthritis. This review will summarize important characteristics of CZP, including efficacy and safety data in psoriasis from pivotal CZP trials, potential benefits for use in pregnant patients, and efficacy and safety in psoriatic arthritis.

Molecular Structure

CZP is the only biologic agent approved for the treatment of psoriasis and psoriatic arthritis that does not contain an IgG Fc region. Rather, it is a TNF-alpha blocker that contains only a PEGylated Fab fragment of a humanized anti-TNF-alpha monoclonal antibody that binds and neutralizes both membrane-bound and soluble TNF-alpha. PEGylation involves covalent conjugation of proteins with polyethylene glycol (PEG), leading to benefits such as increased half-life, increased solubility, and decreased immunogenicity [2]. In addition, another advantage of PEGylation is that CZP is unlikely to be actively transported across the placenta, which requires the Fc portion of the molecule. Consequently, as compared with commonly used agents such as adalimumab, only a small fraction CZP in the maternal circulation is able to enter fetal circulation.

This article is part of the Topical Collection on *Psoriasis*

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Pharmacodynamics and Pharmacokinetics

Pharmacodynamics

CZP binds effectively to both soluble and transmembrane human TNF-alpha. Although PEGylation can decrease antigen binding ability, CZP is PEGylated using site-specific attachment, which allows for PEGylation without affecting CZP's affinity to bind TNF-alpha [3]. Nesbitt et al. conducted in vitro studies in healthy volunteers to compare CZP with other anti-TNF agents. When using the L929 assay system, etanercept was the most potent at neutralizing soluble TNF-alpha, with an IC_{90} (the concentration of a reagent needed to deactivate 90% of the soluble TNF-alpha in the assay) of 0.7 ng/mL, followed by CZP (IC_{90} of 3 ng/mL), then infliximab and adalimumab (each with an IC_{90} of 9 ng/mL) [4]. However, in a second assay using the A549-Luc TNF-alpha-responsive reporter cell assay and recombinant TNF-alpha, CZP showed similar potency to etanercept [4]. When comparing ability to inhibit membrane-bound TNF-alpha, CZP, adalimumab, and infliximab were similar, while etanercept appeared to be about two-fold less potent [2]. Because CZP lacks the Fc portion of the anti-TNF-alpha antibody, it does not cause complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or lymphocyte apoptosis in vitro [4, 5]. As such, CZP may bind to a different epitope from the other agents, leading to a different signaling pattern inside the cell in vivo [3].

When compared with conventional chimeric monoclonal antibodies, CZP is less likely to lead to anti-drug antibody formation [2]. Antibodies produced in response to other anti-TNF agents, including infliximab, adalimumab, and etanercept do not cross-react with CZP. Thus, CZP is a potential alternative treatment for patients who have previously trialed and failed other anti-TNF biologics [2, 6]. When antibody development was studied in psoriasis patients, approximately 19% (54/281) and 8% (22/265) of subjects with psoriasis who received CZP 200 mg every 2 weeks (Q2W) and CZP 400 mg Q2W for 48 weeks, respectively, developed antibodies to CZP [7]. Of the subjects who developed antibodies to CZP, 45% had antibodies that were classified as neutralizing [7]. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy [7].

Pharmacokinetics

Following subcutaneous administration, CZP reaches maximum plasma drug concentration (Cmax) from 54 to 171 h post-injection [7]. CZP has a bioavailability (F) of approximately 80% (ranging from 76 to 88%) following subcutaneous administration compared with intravenous administration [7]. PEGylation delays the metabolism and elimination of CZP via decreased renal clearance, proteolysis, and immunogenicity [8]. As a result, PEGylation increases the terminal plasma elimination half-life (t ½). For CZP, t ½ is 14 days, regardless of dose [7]. Following IV administration to healthy subjects, clearance ranged from 9.21 to 14.38 mL/h [7]. The clearance following subcutaneous dosing in patients with plaque psoriasis was 14 mL/h with an inter-subject variability of 22.2% (CV) [7]. The route of elimination of CZP has not been extensively studied in human subjects, although studies in rats indicate that the major route of elimination of the PEG component is via urinary excretion [6, 7]. Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of CZP. As a result, insufficient data exist to provide a dosing recommendation in patients with clinically significant renal impairment. The authors recommend caution when prescribing CZP to patients with previously documented renal impairment.

Dosage

The FDA-approved dosing for CZP for moderate-to-severe plaque psoriasis does not involve a loading dose. CZP is primarily available as a prefilled 200 mg/mL syringe but is also available as a lyophilized powder for reconstitution and injection. The recommended dosing is two injections (400 mg total, consisting of two 200 mg/mL prefilled syringes) every 2 weeks. An alternative approach is available for patients with a body weight less than or equal to 90 kg. This regimen also begins with 400 mg (two 200 mg/mL prefilled syringes) every 2 weeks; however, after three injections (week 0, week 2, week 4), the provider can decrease the dose to only one syringe (200 mg only) every 2 weeks for maintenance. The decision to use this alternative dosing in appropriate candidates should be based on a provider's judgment. If utilizing the alternative dosing becomes overly complicated, the authors recommend using the preferred regimen.

For psoriatic arthritis, the preferred FDA-approved regimen involves 400 mg (two 200 mg/mL prefilled syringes) every 2 weeks (week 0, week 2, week 4) followed by a maintenance dose of 200 mg every 2 weeks. Additionally, a maintenance dose of 400 mg (two 200 mg/mL prefilled syringes) every 4 weeks can be considered.

Psoriasis Efficacy

The efficacy and safety of CZP was assessed through two pivotal multicenter, randomized, double-blind, placebo-controlled phase 3 trials (CIMPASI-1, CIMPASI-2) and one multicenter, randomized, double-blind placebo-controlled, single-blind etanercept-controlled phase 3 trial (CIMPACT) [9••, 10••]. In CIMPASI-1 ($n = 234$) and CIMPASI-2 ($n = 227$), patients with moderate-to-severe chronic plaque were randomized to CZP 400 mg, CZP 200 mg, or placebo Q2W. In CIMPACT ($n = 559$), CZP 400 mg Q2W was compared

with either placebo Q2W, CZP 200 mg Q2W after 400 mg loading doses at weeks 0, 2, and 4 for 16 weeks, or etanercept 50 mg twice weekly for 12 weeks.

Pooled Psoriasis Area and Severity Index (PASI) 75 (achieving at least a 75% reduction in PASI score when compared with baseline), PASI 90, and Physician Global Assessment (PGA) 0/1 responder rates (clear/almost clear with greater than or equal to 2-point improvement from baseline PGA score) at week 16 for all three studies are summarized in Fig. 1 [11•]. In addition, PASI 75, PASI 90, and PGA 0/1 responder rates at week 12 comparing etanercept 50 mg twice weekly, CZP 200 mg Q2W, and CZP 400 mg Q2W in CIMPACT are shown in Fig. 2 [10••]. At week 12, CZP 400 mg was superior and CZP 200 mg was noninferior to etanercept for PASI 75 responder rate.

Efficacy from Week 16 to Week 48

Pooled data from CIMPASI-1 and CIMPASI-2 of PASI 75, PASI 90, and PGA 0/1 responder rates are shown in Fig. 3 [9••]. Response rates from week 16 were maintained through week 48. In CIMPACT, PASI 75 responder rates for patients initially on CZP 400 mg Q2W following rerandomization was highest for subjects who were continued on CZP 400 mg Q2W (98.0%), followed by patients switched from CZP 400 mg Q2W to CZP 200 mg Q2W (80.0%), and patients switched from CZP 400 mg Q2W to placebo (36.0%) [10••]. PASI 75 responder rates for patients initially on CZP 200 mg Q2W following rerandomization followed a similar trend: 88.6% for the CZP 400 mg Q4W cohort, 79.5% for subjects maintained on CZP 200 mg Q2W, and 45.5% for the placebo group [10••]. Finally, for subjects switched from etanercept to CZP 200 mg Q2W ($n = 50$), PASI 75, PASI 90, and PGA 0/1 at week 48 were 82.0%, 72.0%, and 78.0%, respectively [10••].

Of note, 29.8% of subjects in CIMPACT, CIMPASI-1, and CIMPASI-2 had previously received biologic therapy, including anti-TNF and anti-IL-17 therapy [11•]. In these subjects, PASI 75, PASI 90, and PGA 0/1 responder rates were similar to those in treatment-naive patients. As such, CZP may be an appropriate choice in patients who have failed previous biologic therapies. PASI 75 results of patient with previous biologic exposure are summarized in Fig. 4 [11•].

Sbidian et al. conducted a Cochrane network meta-analysis of 109 randomized control trials published before 2017 of systemic treatments for chronic, moderate-to-severe plaque psoriasis [12]. After reviewing placebo-controlled, head-to-head, and multi-armed active comparator and placebo-controlled studies, the authors concluded that all of the anti-IL17 agents studied (ixekizumab, secukinumab, brodalumab) and guselkumab (anti-IL23) were significantly more effective than the anti-TNF-alpha agents infliximab, adalimumab, and etanercept, but not CZP in achieving PASI 90 [12]. In addition, the authors also concluded that when considering both efficacy (PASI 90) and acceptability (based on number of significant adverse events), ustekinumab, infliximab, and CZP appeared to have better compromise between efficacy and acceptability compared with the other agents studied [12]. Of note however, the meta-analysis only included one study ($n = 176$) using CZP [13] and was conducted prior to CZP receiving FDA approval for psoriasis treatment.

Safety

As with other anti-TNF biologics, the primary concern regarding safety with CZP involves minimizing the risk of tuberculosis (TB) and other granulomatous diseases. This can be accomplished with proper screening for TB prior to initiation of treatment, periodic TB testing throughout CZP treatment course, and maintaining clinical vigilance on the part of the clinician to identify potential TB symptoms and risk factors in patients.

Safety assessment results from CIMPASI-1, CIMPASI-2, and CIMPACT through 48 weeks were comparable to the safety profile of other anti-TNF agents in patients with moderate-to-severe plaque psoriasis and in patients in which TNF blockers were used for other indications [13–16]. The

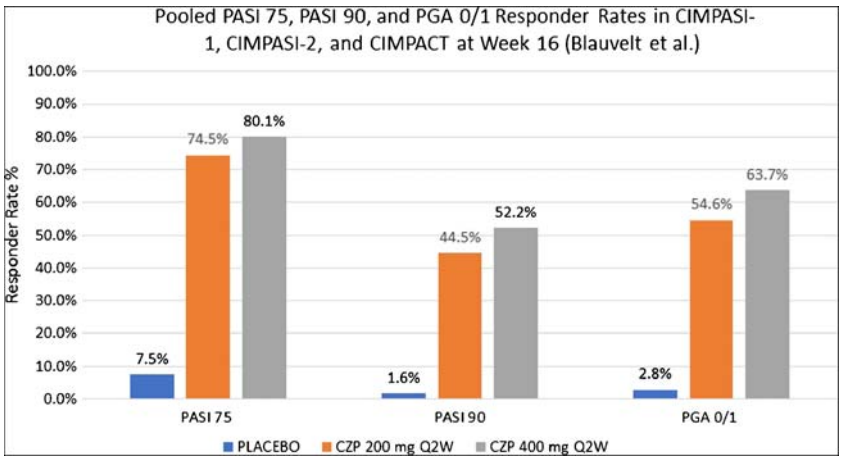

Fig. 1 Pooled PASI 75, PASI 90, and PGA 0/1 responder rates in CIMPASI-1, CIMPASI-2, and CIMPACT at week 16 (Blauvelt et al.)

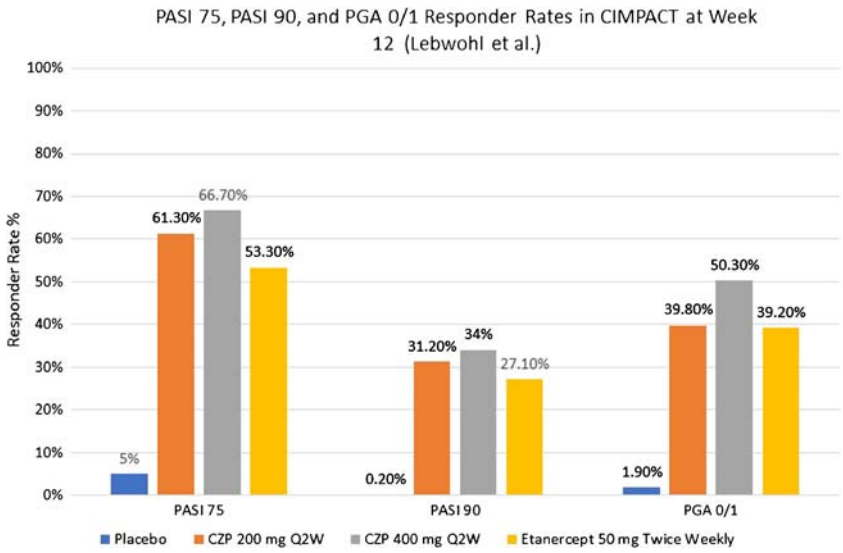

Fig. 2 PASI 75, PASI 90, and PGA 0/1 responder rates in CIMPACT at week 12 (Lebwohl et al.)

most frequently reported treatment-emergent adverse events (TEAEs) in these studies (occurring in greater than or equal to 5% of any CZP treatment group) were nasopharyngitis and upper respiratory tract infections. Incidence rates (new cases per 100 patient-years) for the most frequently reported TEAEs in CIMPACT, CIMPASI-1, and CIMPASI-2 are shown in Table 1 [9••, 10••].

A review of long-term safety data up to August 2017 of 49 UCB-sponsored CZP clinical trials totaling 21,695 patient-years determined that the long-term safety profile across CZP indications was comparable with previous reports and that psoriasis patients had the lowest rates of serious adverse events [17].

Psoriatic Arthritis Efficacy

Anti-TNF agents have long been recognized as one of the most effective classes of medication to treat psoriatic arthritis [18], which affects up to roughly 30% of patients with psoriasis. There are two main components to psoriatic arthritis treatment efficacy. The first involves the extent and speed that a medication works for pain, swelling, and stiffness. The second is the degree to which an agent is capable of mitigating joint destruction and bone erosion. The RAPID-PsA study was a multicenter, 216-week, phase 3 randomized control trial of CZP in patients with psoriatic arthritis [19••]. The trial was placebo-controlled to week 24, dose-blind to week 48, and open-label to week 216. Patients were initially randomized to either placebo, CZP 200 mg Q2W, or 400 mg Q4W (following 400 mg at week 0, 2, and 4). Improvements in disease activity were measured using ACR (American College of Rheumatology) 20/50/70, DAPSA (Disease Activity Index for Psoriatic Arthritis), MDA criteria (minimal disease activity criteria), and VLDA (very low disease activity criteria). For patients with enthesitis, dactylitis, or nail psoriasis at baseline,

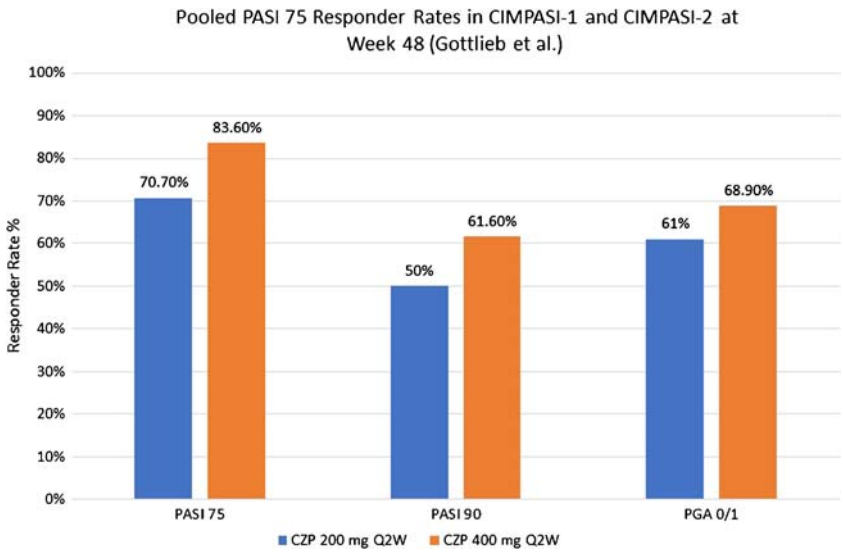

Fig. 3 Pooled PASI 75 responder rates in CIMPASI-1 and CIMPASI-2 at week 48 (Gottlieb et al.)

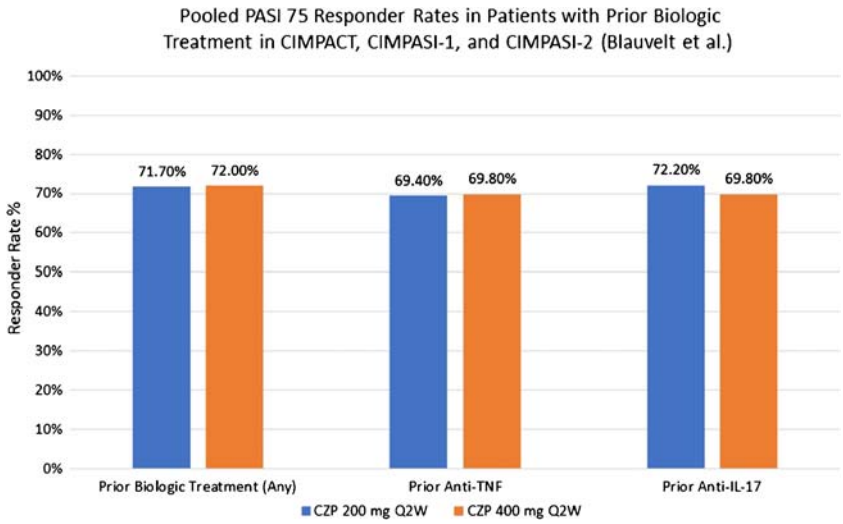

Fig. 4 Pooled PASI 75 responder rates in patients with prior biologic treatment in CIMPACT, CIMPASI-1, and CIMPASI-2 (Blauvelt et al.)

improvement was measured using the Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI), and modified Nail Psoriasis Severity Index (mNAPSI), respectively.

Among patients assessed at week 216, 79.7% of those using CZP with concomitant disease-modifying anti-rheumatic drugs (DMARDs) vs 83.3% using CZP alone achieved an ACR 20 response [20]. In addition, significant improvements in psoriatic arthritis, as measured by ACR 20/50/70, after 24 weeks of CZP treatment were generally maintained throughout the dose-blind and open-label phases and were similar irrespective of prior anti-TNF exposure. ACR 20/50/70 based on non-responder imputation (NRI) at week 24 for patients receiving CZP from week 0 were 60.1%, 43.2%, and 26.4%, respectively [19••, 21]. At week 216, ACR 20/50/70 (NRI) for patients receiving CZP from week 0 were 54.6%, 43.2%, and 34.8%, respectively [19••]. Of the patients who completed CZP treatment to week 216, NRI results showed 19.4% achieved VLDA, 39.2% achieved MDA, and 66.3% achieved either DAPSA remission or DAPSA LDA [19••]. Furthermore, more than two-thirds of patients with baseline involvement of dactylitis, enthesitis, and nail psoriasis went on to achieve total resolution of their respective conditions following treatment with CZP to week 216 [19••]. Finally, radiographic assessments showed minimal structural joint damage progression in patients treated with CZP from week 0 to week 216 and in patients originally randomized to placebo, who were re-randomized to CZP at week 16 or 24 [19••].

Certolizumab and Pregnancy

Pregnancy is known to affect psoriasis severity with 41% of patients experiencing an increase in body surface area (BSA) involvement postpartum [22]. During pregnancy, trans-placental migration of maternal antibodies requires recognition of the Fc portion by the neonatal Fc receptor. Given that CZP lacks this portion, significant transfer of the CZP monoclonal antibody is unlikely. This has been verified by two pharmacokinetic studies that have analyzed placental transfer of CZP [23, 24]. In addition, one pharmacokinetic study has examined transfer of CZP in breastmilk [25]. Mahadevan et al. compared serum concentrations of CZP, infliximab, and adalimumab

Table 1 Most frequently reported TEAEs, *n* (%) (incidence rate, new cases/100 patient-years) in CIMPACT, CIMPASI-1, and CIMPASI-2 from baseline to week 48 (Lebwohl et al., Gottlieb et al.)

	CIMPACT		CIMPASI-1		CIMPASI-2	
	CZP 200 mg Q2W (*n* = 265)	CZP 400 mg Q2W (*n* = 354)	CZP 200 mg Q2W (*n* = 100)	CZP 400 mg Q2W (*n* = 144)	CZP 200 mg Q2W (*n* = 95)	CZP 400 mg Q2W (*n* = 129)
Nasopharyngitis	35 (13.2) [23.6]	44 (12.4) [22.6]	28 (28.0) [46.4]	40 (27.8) [46.9]	17 (17.9) [26.4]	25 (19.4) [29.0]
Upper respiratory tract infection	16 (6.0) [10.5]	29.(8.2) [14.4]	12 (12.0) [17.2]	13 (9.0) [12.8]	11 (11.6) [16.1]	13 (10.1) [14.5]
Hypertension	10 (3.8)[6.5]	17 (4.8) [8.3]				
Viral upper respiratory tract infection	14 (5.3) [9.1]	8 (2.3) [3.8]				

in pregnant women with inflammatory bowel disease to serum concentrations in infants at birth and in cord blood. Enzyme-linked immunosorbent assay (ELISA) revealed that concentrations of infliximab and adalimumab, but not CZP, were higher in infants and in cord blood than in their mothers [24]. The levels of CZP in infants and in cord blood were less than 2 micrograms per milliliter [24]. The CRIB study, which specifically examined pregnant patients using CZP, similarly found minimal to no transfer of CZP from mother to infant when using an electrochem iluminescence immunoassay sensitivity and specific to CZP [23]. The CRADLE study examined 137 breast milk samples in patients receiving either CZP 200 mg Q2W ($n = 16$) or CZP 400 mg Q4W ($n = 1$). The study determined that all samples had CZP concentrations that were minimal or below the lower limit of quantification [25]. In addition, 56% of samples had no measurable CZP and the highest CZP concentration (0.076 micrograms per milliliter) was less than three times the lower limit of quantification (0.032 μg/mL) [25]. Based on the results of these studies, CZP may appeal to pregnant patients or patients of childbearing potential who express concerns about the risk of exposure of biologic agents to the fetus or to the breastfeeding infant. There are two important caveats to consider however. First, these studies, while demonstrating minimal transfer of CZP to the placenta and in breast milk, do not directly provide safety and efficacy data of CZP in pregnant women or in breastfeeding infants. Second, the decision to start or switch to a particular biologic agent is multifactorial, and while a provider may consider pregnancy when choosing a biologic, other factors such as disease severity, insurance restrictions, and frequency of drug administration should be considered as well.

Conclusion

CZP has several advantages, including efficacy for psoriasis, first-rate efficacy for psoriatic arthritis, and potential benefits in avoiding in utero and postpartum biologic exposure for women of childbearing potential. Furthermore, patients with previous biologic exposure in pivotal psoriasis and psoriatic arthritis trials have demonstrated clinical improvement while on CZP. As a result, providers may consider using CZP in patients who are not biologic naive. Given that CZP has been in human use for over 20 years, it may also be appealing to patients who are more comfortable with medications that have long-term safety data. Providers should consider all the potential benefits and risks of available options to patients prior to selecting a specific treatment. In addition, this decision should be a shared decision between provider and patient that balances patient preference, ease of use, efficacy, and safety.

Compliance with Ethical Standards

Conflict of Interest Dr. John Koo is on the Speaker's Bureau for UCB and serves as an advisor. Drs. Vidhatha Reddy and Quinn Thibodeaux declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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