Efficacy and safety of certolizumab pegol in pregnant women with uveitis. Recommendations on the management with immunosuppressive and biologic therapies in uveitis during pregnancy

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Abstract

Objective

Clinicians often face the challenge of providing effective and safe therapy for pregnant women with uveitis. Certolizumab pegol (CZP) differs from other anti-TNFα agents due to its limited placental transfer. In this study we assessed the efficacy of CZP in pregnant women with uveitis. We also provided information on outcomes of pregnant women and neonates exposed to CZP.

Methods

We carried out a multicentre study of women with uveitis who received CZP during pregnancy and their neonates. The main visual outcomes were visual acuity (VA), intraocular inflammation and corticosteroid-sparing effect. Pregnancy outcomes, maternal and neonatal infections and congenital malformations were also assessed.

Results

We studied 14 women (23 affected eyes); mean age of 34.3±5.5 years. The underlying diseases were spondyloarthritis (n=7), idiopathic (n=2), and Vogt-Koyanagi-Harada, rheumatoid arthritis, juvenile idiopathic arthritis, punctate inner choroidopathy and Behçet's disease (1 each). The patterns of ocular involvement were anterior (n=10), posterior (n=2), intermediate (n=1), panuveitis (n=1). Cystoid macular oedema was present in one patient (1 eye). Uveitis was bilateral in nine cases and chronic in seven patients. CZP was started before getting pregnant in ten patients and after conceiving in four. All patients achieved or maintained ocular remission throughout pregnancy. Fifteen healthy infants were born. Only one woman presented a mild infection during pregnancy. Neither infections nor malformations were observed in neonates after a follow-up of 6 months. Six infants were breastfed and all of them received scheduled vaccinations without complications.

Conclusion

Certolizumab pegol is effective and safe in women with uveitis during pregnancy.

Key words

certolizumab, uveitis, pregnancy, safety, efficacy

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Competing interests: see page 112.

Introduction

Non-infectious uveitis is a relatively common inflammatory condition that can lead to irreversible blindness. Uveitis may occur at any age but is most often observed in patients aged 20 to 50 years. This is especially true for HLA-B27 associated acute anterior uveitis that predominantly affects young adults at a mean age of about 35 years old and juvenile idiopathic-associated uveitis which often remains active in the early adulthood (1-3). Therefore, uveitis is a potentially sight-threatening condition that can affect young individuals who are in their reproductive years.

Management of uveitis in the periconceptional period and pregnancy is cause of great concern for patients and physicians. It is well-known that maternal disease activity is associated with a higher risk of adverse gestational outcomes. Thus, effective therapy is needed to ensure sustained remission during pregnancy. However, the use of most therapies is limited in pregnant patients due to the lack of safety data (4).

The understanding of the course of the ocular inflammatory disease during pregnancy may be of great help to provide an adequate therapy. In this regard, it has been reported that pregnancy can have a beneficial effect in some systemic inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). Meanwhile, other entities such as systemic lupus erythematosus (SLE) usually flare during pregnancy leading to a higher risk of complications such as thrombosis, miscarriage, preeclampsia and premature delivery. There is no consensus on the effect of pregnancy in Ankylosing Spondylitis (AS), but it is generally accepted that it does not improve the symptoms of AS or even worsens them (5-8). Unfortunately, the influence of pregnancy on the course of non-infectious uveitis has not been thoroughly studied. Available evidence suggests that there is an initial increase in uveitis activity at pregnancy onset that progressively decreases to the lowest activity in the third trimester. However, the postpartum period has been associated with a rebound of flare rates (9-13).

Clinicians often face the challenge to re-consider therapy options for women with uveitis when they manifest reproductive desire or are already pregnant. Unfortunately, there are no global guidelines for the management of uveitis during pregnancy and most current insights come from case reports since no clinical trials have been performed due to ethical considerations. According to most authors, it is recommended the addition of conventional disease-modifying anti-rheumatic drugs (cDMARDs) when high doses of systemic glucocorticoids are needed to control the ocular inflammation. However, it is important to avoid methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide (4, 13-15). Biologic therapy should be considered when conventional therapy fails. With respect to this, the safety of anti-tumour necrosis factor alpha (anti-TNF-α) therapy during pregnancy has been addressed in some recent reviews, although most data come from studies on inflammatory bowel disease (16-18). According to the last EULAR guidelines for the use of anti-rheumatic drugs during pregnancy (19), infliximab (IFX) and adalimumab (ADA) may be preferentially stopped at 20 weeks and etanercept (ETN) at 30–32 weeks of pregnancy. In keeping with this, the British Society for Rheumatology guidelines (4) proposed that IFX may be continued until 16 weeks of pregnancy and ETN and ADA until the end of the second trimester. Golimumab (GOLI) seems to be also safe during the first trimester but there are not data on its use during the second and third trimester. In contrast, certolizumab pegol (CZP) may be used throughout the pregnancy and breastfeeding due to its limited placental transfer.

CZP differs from other anti-TNF-α agents in the absence of Fc-region, which is known to play a key role in materno-foetal placental transfer by binding to the neonatal Fc receptor (FnRn) (20). As a Fc-free agent, CZP does not bind FnRn and, therefore, it cannot be actively transported across the placenta (21-24). This confers advantageous properties to CZP in pregnant patients making it a safe option during pregnancy as it was recently reported in a

retrospective study involving more than a thousand of women (25). In addition, CZP has shown efficacy in the management of refractory non-infectious uveitis in off-label use in two recent observational studies (26, 27). However, clinical data on the use of CZP in patients with uveitis during pregnancy are absent.

Taking all these considerations into account, our aims were to assess the efficacy of CZP in pregnant patients with uveitis and to provide information on the pregnancy outcomes of women and neonates who were exposed to CZP. In addition, a literature review of the treatment of uveitis during pregnancy was conducted.

Patients and methods

Study design

We conducted a national multicentre, observational, case series study in patients diagnosed with uveitis who received CZP during pregnancy as well as on the infants who were exposed to CZP from July 2013 to September 2019. A minimum follow-up of 6 months after birth was required for inclusion. Data regarding demographics, ocular inflammatory processes, systemic inflammatory disease diagnosis, previous treatments, pregnancy, delivery and health of neonates were collected. All data were gathered and analysed according to the agreed protocol. Patients were studied at the outpatient clinics of the Uveitis Units of several referral centres. Uveitis was anatomically classified according to the Standardization of Uveitis Nomenclature (SUN) Working Group (28). All systemic inflammatory disease diagnoses were made by experienced rheumatologists according to the available classification criteria for each disorder.

Since CZP is an off-label indication for uveitis, written informed consent was requested and obtained from all the patients before starting therapy. Patients were treated with CZP as monotherapy or combined with conventional immunosuppressive drugs. CZP was used at the standard dose of 400 mg at weeks 0, 2 and 4, then continued as 400 mg injections monthly, or 200 mg injections every other week.

Remission was defined as the absence of active intraocular inflammation for at least 3 months. Intraocular inflammation included the following features; anterior or posterior chamber inflammation, retinal vasculitis, papillitis and cystoid macular oedema (CME). A relapse was considered when an asymptomatic patient experienced a new flare of uveitis.

Visual outcomes

The main outcome measures were visual acuity, intraocular inflammation and sparing glucocorticoid effect. These outcome variables were recorded in each centre according to a predefined protocol at baseline, 1 and 2 weeks; 1, 3 and 6 months; and 1, 2 and 3 years after CZP onset.

The degree of intraocular inflammation was assessed according to the SUN Working Group (28). The Nussenblat scale was used to evaluate the degree of vitritis (29). Visual acuity (VA) was expressed as the best-corrected visual acuity (BCVA) using the Snellen chart. For the purpose of the present study, 20/20 (normal vision) was expressed as 1.0 and 0/20 as 0.0. Inactive anterior uveitis was defined as <1 cell per field in the anterior chamber (AC) on slit lamp examination (grade 0). Similar definition was used for the degree of vitritis. Retinal vasculitis was defined as retinal angiographic leakage, staining and/or occlusion on fluorescein angiogram. Choroiditis and retinitis were considered active or inactive depending on the presence or absence of activity data on the ophthalmic examination and/or in the fluorescein angiogram. Macular thickness was measured by high-definition optical coherence tomography (HD-OCT). All HD-OCT scans were performed using Cirrus HD-OCT (Carl Zeiss, Dublin, CA, USA). Scans were obtained using the 512x128 scan pattern. Macular thickening was defined as a macular thickness >250 μm, and CME was considered to be present when it was >300 μm.

Pregnancy, birth and neonatal outcomes

Pregnancy, birth and neonatal outcomes were abstracted from the medical records.

We collected characteristics of the mother at the time of conception: age, systemic inflammatory disease diagnosis, time of evolution of the inflammatory disease and type of gestation (single or multiple). We also assessed information on exposure to CZP (before and/or after conception) considering the trimesters of exposure. Trimesters of pregnancy were determined as follows, first trimester up to 12 weeks and 6 days, second trimester from 13 weeks to 28 weeks and 6 days, and third trimester as any time including and after 29 weeks.

The presence of complications during pregnancy and delivery were also assessed, including miscarriages, maternal infections, pre-eclampsia and premature rupture of membranes. Birth outcomes assessed included estimated gestational age at delivery (calculated by last menstrual period or ultrasound dating), mode of delivery (vaginal/cesarean), birth weight and height, foetal pH, Apgar score and congenital malformations. A normal value of foetal pH was considered if pH >7.25 (30). The Apgar score provides an accepted and convenient method for reporting the status of the newborn infant immediately after birth and the response to resuscitation if it is needed. The Neonatal Encephalopathy and Neurologic Outcome defines a 5-minute Apgar score of 7 to 10 as reassuring, a score of 4 to 6 as moderately abnormal, and score of 0 to 3 as low in term infant and late-preterm infant (31).

After 6 months, health outcomes from children were obtained through telephonic questionnaire to the parents and/or by obtaining medical information from the general practitioner after parental consent. We assessed data regarding infections that required systemic antibiotic treatment and/or hospitalisation, breastfeeding and vaccine administration. The national immunisation schedule for infants in Spain includes the following vaccines to be administered in the first 6 months of live: hepatitis B, diphtheria, tetanus and acellular pertussis (DTaP), inactivated poliovirus (IPV), Haemophilus influenzae type B conjugate (Hib), pneumococcal conjugate (PCV) and meningococcal C conjugate (MenC). Rotavirus (RV) and

Table I. Baseline characteristics of the 14 pregnant women diagnosed with uveitis and receiving CZP.

Case	Age (yrs. at CZP onset)	Underlying disease	Uveitis pattern	Laterality	Immunosuppressive drugs before CZP	Combined treatment during pregnancy
1	34	SpA	Anterior	Unilateral	MTX, AZA, ADA	Yes (AZA)
2	37	SpA	Anterior	Bilateral	MTX, AZA, IFX, ADA, GOLI	No
3	39	SpA	Anterior	Bilateral	AZA, ADA	Yes (AZA)
4	46	SpA	Anterior	Unilateral	CyA, ETN, ADA, IFX, GOLI	No
5	32	SpA	Anterior	Unilateral	SSZ, ADA	Yes (SSZ)
6	36	SpA	Anterior	Bilateral	MTX, HCQ, ADA	No
7	40	SpA	Anterior	Bilateral	MTX, LFN, HCQ, IFX, ADA, GOLI	Yes (HCQ)
8	31	Idiopathic	Intermediate	Bilateral	MTX, MMF, CyA, ADA	No
9	33	Idiopathic	Anterior	Unilateral	MTX, AZA, ADA, ETN	No
10	32	Rheumatoid arthritis	Anterior	Unilateral	MTX	Yes (AZA)
11	23	Vogt-Koyanagi-Harada	Panuveitis	Bilateral	AZA, ADA	Yes (AZA)
12	36	Juvenile idiopathic arthritis	Anterior	Bilateral	ADA	No
13	32	Punctate inner choroidopathy	Posterior	Bilateral	ADA	No
14	29	Behçet's disease	Posterior	Bilateral	CyA, IFX, ADA	No

ADA: adalimumab; AZA: azathioprine; CyA: cyclosporine A; ETN: etanercept; GOLI: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; LFN: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; SpA: spondyloarthritis; SSZ: sulfasalazine.

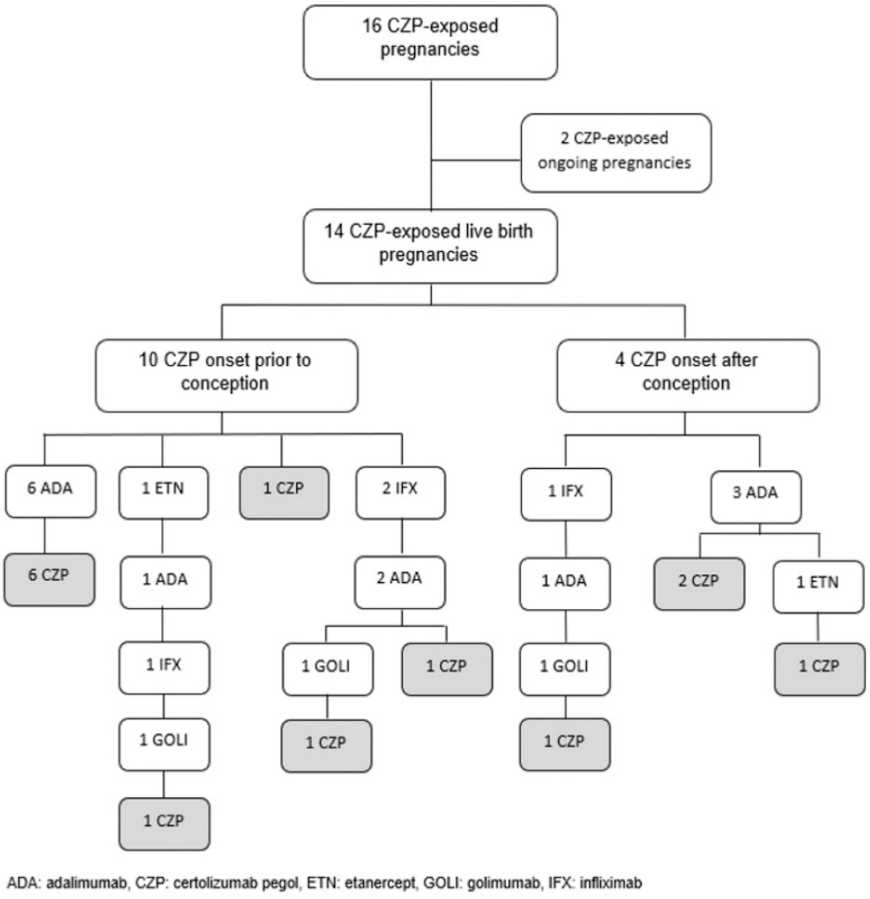

Fig. 1. Flow-chart of the CZP-exposed pregnant women showing the biologic agents prescribed to these patients prior to CZP therapy.

meningococcal B (MenB) vaccination has no public funding in Spain (32).

Ethics

The study was approved by the Local Institutional Review Board (IRB no. 2018-110). Parents or legal guardians of the children signed informed consent before data was collected from the general practitioner.

Statistical analysis

The statistical analysis was performed using SPSS Statistics for Windows, v. 18.0 (SPSS Inc, Chicago, IL, USA). All continuous variables were tested for normality, and results were expressed as mean ± SD or as median and interquartile range (IQR) as appropriate. Student's t-test or Mann-Whitney U-test were used to compare continuous variables, and chi-squared test for categorical variables. The comparison of continuous variables among time periods was performed using the Wilcoxon signed rank test. A p-value <0.05 was considered as statistically significant in all the calculations.

Results

Sixteen women (26 affected eyes) with uveitis who received CZP during pregnancy were enrolled in the study. At the end of the study period (September 1, 2019), 2 of these patients were still pregnant and they were therefore excluded from the analysis. The remaining 14 women (23 affected eyes) resulted in 15 live births and were included in the analysis after a follow-up of at least 6 months after birth.

Baseline data at CZP onset

The median age at CZP onset was 34.3±5.5 years. The underlying diseases were spondyloarthritis (n=7), idiopathic (n=2), Vogt-Koyanagi-Harada (n=1), rheumatoid arthritis (n=1), juvenile idiopathic arthritis (n=1), punctate inner choroidopathy (n=1), Behçet's disease (n=1). The patterns of ocular uveitis were anterior (n=10), posterior

(n=2), intermediate (n=1), panuveitis (n=1). CME was present in one patient (one eye). Uveitis was bilateral in 9 cases. The clinical course was chronic in half of the patients. The main baseline epidemiological and clinical features of the 14 patients who were included for the analysis are shown in Table I.

Previous immunosuppressive agents before CZP

Before CZP onset and besides oral glucocorticoids all patients had received cDMARDs: methotrexate (n=7), azathioprine (AZA) (n=5), cyclosporine A (CyA) (n=3), sulfasalazine (SSZ) (n=1), hydroxychloroquine (n=1), leflunomide (n=1), mycophenolate mofetil (n=1). Thirteen of them had also received biologic therapy: ADA (n=13), IFX (n=4), GOLI (n=3), ETN (n=2). In one patient CZP was the first biologic agent. Figure 1 shows the biologic agents prescribed to these patients prior to CZP.

Clinical efficacy of CZP

The reasons given by the clinicians in charge of the patients to start CZP therapy were the following: desire for pregnancy (n=6), current pregnancy (n=4), refractoriness to previous treatment (n=3) and adverse reaction to previous treatment (n=1). CZP was initiated prior to conception in 10 patients and at the end of the first trimester of pregnancy in the remaining 4 patients. CZP was administered as monotherapy in 8 patients and combined with conventional immunosuppressive drugs in the remaining 6 patients (azathioprine in 4 and sulfasalazine and hydroxychloroquine in 1 each). At the onset of CZP therapy six patients were taking oral glucocorticoids. Following CZP therapy, all patients were able to reduce the prednisone (or equivalent) dose progressively from a mean dose at baseline of 21.719.7 mg/day to 4.1±3.8 mg/day at 6 months (p=0.03), leading to complete discontinuation in 4 of them. Overall, after a median follow-up of 26.8±18.1 months patients experienced an improvement of the BCVA (0.73±0.20 to 0.85±0.20; p=0.045) and the number of chamber cells decreased from a median of 1.0 [0.0-3.0] to 0.0 [0.0-0.0] (p=0.041) (Fig. 2). At baseline 2 patients had active vitritis. At month 6, all patients had a grade 0 score in Nussenblat scale. One patient had active choroiditis at baseline which re-

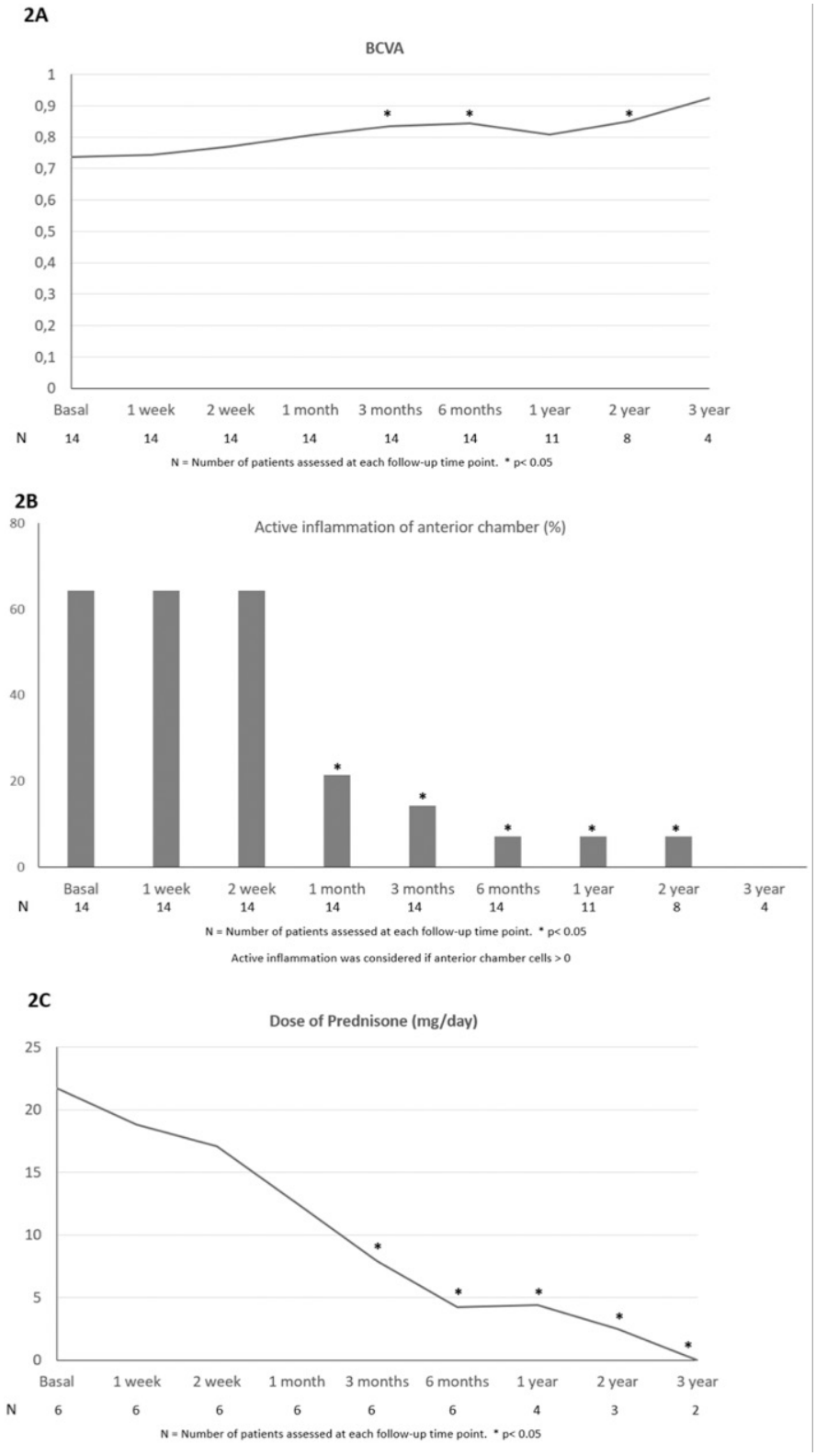

Fig. 2. Outcome of ocular parameters and prednisone dose following CZP therapy.
A: Best-corrected visual acuity (BCVA).
B: Anterior chamber cells (AC cells). Active inflammation was considered if AC cells >0.
C: Corticosteroid-sparing effect (values are expressed as the mean of prednisone equivalent dose/day).

Table II. Pregnancy and neonatal outcomes of the newborns.

	Gestational age	Multiple gestations	Preconception CZP exposure	Trimesters of CZP exposure	Labour complications	Maternal infections	Neonatal infections (<6 mo. after birth)	Congenital malformations	Breast-feeding
1	Full-term	No	Yes	1,2,3	No	No	No	No	No
2	Full term	No	No	2,3	No	No	No	No	No
3	Full term	Yes (dichorionic)	No	2,3	No	No	No	No	No
4	Full term	Yes (dichorionic)	No	2,3	No	No	No	No	No
5	Full-term	No	Yes	1,2,3	No	No	No	No	No
6	Full term	No	No	2,3	No	No	No	No	Yes
7	Full-term	No	No	2,3	No	Yes	No	No	Yes
8	Full-term	No	Yes	1,2,3	No	No	No	No	Yes
9	Full-term	No	Yes	1,2,3	No	No	No	No	No
10	Full-term	No	Yes	1,2,3	No	No	No	No	Yes
11	Full-term	No	Yes	1,2,3	No	No	No	No	No
12	Full-term	No	Yes	1,2,3	No	No	No	No	Yes
13	Full-term	No	Yes	1,2,3	No	No	No	No	Yes
14	Full-term	No	Yes	1,2,3	No	No	No	No	No
15	Full-term	No	Yes	1,2,3	No	No	No	No	No

Table III. Recommendations regarding infant vaccination after exposure to anti-TNF-α agents during pregnancy according to the European Summary of Product Characteristics (SmPC) Label Information.

Anti-TNF-α agent	Inactivated vaccines	Live vaccines	Reported complications after live vaccines administration
Infliximab	Allowed	Not recommended for at least 6 months after birth.	Disseminated BCG in a newborn who received the BCG vaccine at 3 months of age.
Adalimumab	Allowed	Not recommended for 5 months following the mother's last dose.	
Etanercept	Allowed	Not recommended for 16 weeks following the mother's last dose.	
Golimumab	Allowed	Not recommended for 6 months following the mother's last dose.	
Certolizumab	Allowed	Not recommended for 5 months following the mother's last dose, unless the benefit of vaccination clearly outweighs the theoretical risk of administration of live vaccines.	

solved within the second week. CME was present in one patient (one eye), which remained stable within CZP therapy (OCT decreased from 314 to 305 μm after 6 months of CZP onset).

Overall, 12 patients obtained a sustained ocular remission. In all patients in whom CZP was initiated before getting pregnant (n=10), sustained remission was achieved and/or maintained before they become pregnant and also throughout pregnancy. However, one of them suffered a relapse after 24 months of CZP therapy and had to be switched to ADA. In one patient CZP was discontinued due to sustained disease remission after 26 months of treatment. With respect to the patients in whom CZP was started during pregnancy (n=4), three of them had active disease at the time of CZP onset. All of them achieved remission during pregnancy and post-partum periods. However, CZP had to be withdrawn in one of them due to a relapse that occurred after 8 months of treatment and she was switched to GOLI. CZP was discontinued in another 2 patients because refractory joint disease after 9 and 8 months, respectively. In another patient CZP had to be withdrawn due to a skin reaction after 12 months from CZP onset.

It is also worth noting that the two patients undergoing CZP therapy who were excluded from the analysis due to ongoing pregnancy also remained in clinical remission at the end of the study.

Pregnancy, birth and neonatal outcomes

There was only one case of multiple gestation (dichorionic). Therefore, 15 infants were born to 14 CZP-exposed pregnant women with uveitis. Pregnancy and neonatal outcomes are shown in Table II. The mean age of the mothers at the time of conception was 35.7±4.3 years. CZP was initiated in 10 of them before pregnancy (median of 9.5 [4.0–19.0] months prior to conception). Because of that, 10 newborns were exposed to CZP during the first, second and third trimesters while the remaining 5 neonates were exposed to CZP only during the second and third trimesters. Neither pregnancy nor delivery complications such as pre-eclampsia, eclampsia, premature rupture of membranes, miscarriages or pre-term births were reported. The median gestational age was 37.9±0.9 weeks. Cesarean delivery occurred in 7 patients. All neonates were healthy newborns with a mean birth weight of 3,025±471 grams and a mean length birth of 50.6±2.5 cm with one of the infants defined as low birth weight (<2,500 grams). Foetal pH was normal (pH >7.25) in all neonates. Apgar score

Table IV. Compatibility of common drugs used in uveitis within periconceptional period, pregnancy and breastfeeding.

Drugs	Compatible preconception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding
Non-steroidal anti-inflammatory drugs				
Non-selective COX inhibitors	Yes	Yes	Only during 2nd trimester	Yes
Selective COX-II inhibitors	No	No	No	No Only celecoxib is compatible (#)
Systemic Glucocorticoids				
Prednisone/prednisolone	Yes	Yes	Yes	Yes Monitoring if PD dose > 40 mg/day
Methylprednisolone	Yes	Yes	Yes	
Antimalarials				
Hydroxychloroquine	Yes	Yes	Yes	Yes
Synthetic conventional immunosuppressants				
Azathioprine ≤2 mg/kg/day	Yes	Yes	Yes	Yes
Methotrexate ≤20 mg/week	Stop 3-4 months before pregnancy	No	No	No
Sulfasalazine	Yes	Yes	Yes	Only in healthy full-term infants
Leflunomide	Cholestyramine washout	No	No	No (#)
Mycophenolate mofetil	Stop 6-12 weeks before pregnancy	No	No	No
Cyclosporin A	Yes	Yes	Yes	Yes
Anti-TNF-α agents				
Infliximab	Yes	Yes	Stop at 20 weeks (#) Stop at 16 weeks (*)	Yes
Adalimumab	Yes	Yes	Stop at 20 weeks (#) Stop at the end of 2nd trimester (*)	Yes
Etanercept	Yes	Yes	Stop at 30-32 weeks (#) Stop at the end of 2nd trimester (*)	Yes
Golimumab	No data	No data	No data	Yes (#)
Certolizumab	Yes	Yes	Yes	Yes
Other biological therapies				
Tocilizumab	Stop 3 months before pregnancy (*)	No	No	No (#)
Ustekinumab	No data	No data	No data	No
Tofacitinib	Stop 2 months before pregnancy (#)	No (#)	No (#)	No (#)

Adapted from Table IV (Götestam Skorpen C *et al*.: *Ann Rheum Dis* 2016; 75: 795-810) and Table I (Flint *et al*.: *Rheumatology* (Oxford) 2016; 55: 1693-7).
#following EULAR Guideline recommendations; *following British Guideline recommendations; PD: prednisone/prednisolone.

was above 8 in all of them. Six of 15 neonates were breastfed, and the mothers of these infants continued to receive CZP in the post-partum. With regard to infections, only one woman presented a mild urinary tract infection during pregnancy. Neither infections nor malformations occurred in the infants after a follow-up of 6 months. All infants received inactivated vaccines as scheduled in the national immunisation programme. One of them also received rotavirus vaccine with no complications.

Discussion

Management of severe non-infectious uveitis can represent a major challenge in pregnant patients. Clinicians face the difficulty of keeping the mother in remission to have a successful pregnancy while avoiding treatments that can be harmful for the foetus (33). In this regard, we report 14 cases of pregnant women with uveitis who achieved a favourable and sustained ocular response to CZP during pregnancy giving birth to 15 healthy infants. To the best of our knowledge, this is the first series published to date on pregnant women with uveitis treated with CZP.

Our results support the efficacy of CZP for the management of uveitis during pregnancy. Patients in whom CZP was

initiated before pregnancy and also those who were switched to CZP during pregnancy (at the end of the first trimester) from ADA (n=2), GOLI (n=1) and ETN (n=1) remained in remission throughout pregnancy and post-partum period. These results are in keeping with the scarce available literature addressing the efficacy of CZP in uveitis. In this regard, Llorenç *et al*. (27) reported complete remission in 5 of 7 cases of long-lasting chronic-relapsing uveitis with prior failure to anti-TNF-α drugs treated with CZP. Rudwaleit *et al*. (34) observed a 3 time-lower rate of uveitis flares in comparison with the placebo group in a series of spondyloarthritis treated with CZP during a 24-week period. Recently, Tosi *et al*. (26) reported a significant reduction of ocular flares with a good long-term retention rate in 11 patients with refractory uveitis who received CZP. With respect to this, Berkhout *et al*. (35) have recently observed a higher relative *in vitro* TNF neutralising potency of CZP compared to ADA which correlated with CZP serum concentration.
Dose reduction and duration of glucocorticoids is a priority in pregnancy (36). Interestingly, a rapid and maintained decrease of prednisone dose was achieved in our patients.
In terms of pregnancy-safety, CZP displays advantageous properties over other anti-TNF-α agents due to its limited transport across the placenta as it has been demonstrated in an *in vivo* rodent model, an *ex vivo* human placental model and in three recent studies in humans (21-23, 37, 38). The Union Chimique Belge (UCB) Pharma safety database showed a lack of harmful effect of CZP-maternal exposure in 1137 prospectively reported pregnancies (25). Our results support these findings. No congenital malformations were reported, considering that most pregnancies (10/14) were exposed to CZP during the first trimester when organogenesis primarily occurs. In the UCB Pharma safety database (25), frequencies of serious maternal infections (4.2%) and preeclampsia (1.1%) were comparable to those in general population as well as to our series.
In a recent meta-analysis, neither increase of preterm birth nor low birth weight was found in anti-TNF-α exposed infants (39). Our results are in line with these findings. There are some concerns about a higher risk of neonatal infections in patients exposed to IgG1 TNF-α agents (such as ADA and IFX) (40, 41). However, according to the data provided by the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, CZP appears to be safe (42, 43). During the first 6 months of live follow-up, no infections requiring hospitalisation or systemic antibiotic therapy were reported in our series of 15 CZP maternal-exposed infants.
According to previous studies, infants exposed to anti-TNF-α agents during pregnancy have adequate vaccination responses (44, 45, 46). In our series, all infants successfully received inactive vaccines following the National immunisation schedule as it is recommended by The Center for Disease Control and Prevention (47).
Recommendations regarding live vaccines administration are controversial. According to the EULAR recommendations (19) and the latest versions of the Summary of Product Characteristics (SmPC) of each anti-TNF alfa agent (48), children exposed to biologic therapy at the late second and during the third trimester should not receive live vaccines within the first 6 months of life (Table III). However, some authors suggest avoiding life vaccines during the first year of life or until drug clearance is confirmed (46). These concerns come from a fatal neonatal death due to disseminated BCG infection in an infant exposed to peripartum IFX (49). Regarding rotavirus vaccines, some mild reactions have been reported in infants born to mothers exposed to biologic therapy, except for those whose mothers received CZP (46). Noteworthy, in our series, one infant received rotavirus vaccination with no complications.
Regarding breastfeeding, current data suggest that anti-TNF-α therapy is compatible with lactation (50-52). Reassuringly, Clowse *et al*. (53) found that levels of CZP were undetectable in most of the breast milk samples of mothers on CZP. This could be explained by the presence of FnRn in the epithelial cells of the human mammary gland (54). In our series, six infants were successfully breastfed.
At the time of making a decision about therapy during pregnancy in patients with uveitis, it is necessary to consider the possible harmful effects of some agents (13, 14). Due to this, we also reviewed the compatibility of the common immunosuppressive drugs used in uveitis with pregnancy and breastfeeding (Table IV). Anti-TNF agents have demonstrated to be relatively safe, although CZP seems to provide the safest profile throughout the three trimesters of pregnancy and breastfeeding.
In conclusion, CZP proves to be effective and safe in patients with uveitis during pregnancy. We support its use as the anti-TNF-α agent of choice in women with uveitis who are pregnant or who manifest reproductive desire.

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The remaining authors declare do not have conflict of interest.

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