Clin Exp Dermatol 2024; **49**:344–347
https://doi.org/10.1093/ced/llad386
Advance access publication date: 13 November 2023

CED
Clinical and Experimental Dermatology
Original Article

Safety of omalizumab in chronic urticaria during pregnancy: a real-life study

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Abstract

Background Managing a pregnant patient with chronic spontaneous urticaria (CSU) is often challenging. Recent data have shown that most CSU treatments in pregnant patients are second-generation H1 antihistamines (sgAHs), while data on the safety of omalizumab are scant.

Objectives To evaluate, in a routine clinical practice setting, the efficacy and safety of omalizumab in patients with severe CSU refractory to sgAHs who either became pregnant during treatment or who started the drug during pregnancy.

Methods We conducted a retrospective study of women aged ≥ 18 years who were pregnant, who received one or more doses of omalizumab at any time during their pregnancy or who were taking omalizumab at the time of, or in the 8 weeks before, conception.

Results Twenty-nine pregnant patients were evaluated: 23 (79%) conceived a child while taking omalizumab (group A), while 6 (21%) started omalizumab treatment during pregnancy (group B). Among patients in group A, we observed 23 births (21 liveborn singletons and 1 liveborn twin pair) and 1 miscarriage. Fifteen (65%) patients discontinued omalizumab after confirming their pregnancy, while eight (35%) were exposed to omalizumab during their entire pregnancy. In group B, omalizumab was introduced at a mean (SD) 10.83 (3.60) weeks' gestation and all patients were exposed to it until the end of pregnancy. In this group, there were seven liveborn infants (five singletons and one twin pair). No adverse events, pregnancy complications or congenital anomalies in newborns were recorded in either group.

Conclusions Omalizumab for CSU treatment before and during pregnancy does not appear to have negative effects on maternal or fetal outcomes.

What is already known about this topic?

- Data on chronic spontaneous urticaria treatment choices and their safety on conception, pregnancy and pregnancy outcomes are limited.
- Current guidelines suggest the same therapeutic approach for pregnant and other patient categories.

What does this study add?

- Omalizumab exposure in women who started therapy during pregnancy, or who took the drug at the time of conception and continued it throughout pregnancy, does not appear to be associated with an increased risk of adverse events (AEs), pregnancy-related AEs or AEs in newborns.

Accepted: 3 November 2023

Omalizumab is a recombinant humanized $IgG1_K$ monoclonal antibody that selectively binds to human IgE.[1] It is recommended for the treatment of adults with moderate-to-severe persistent asthma inadequately controlled with inhaled corticosteroids, for antihistamine-resistant chronic spontaneous urticaria (CSU) and for the maintenance treatment of nasal polyps in adults aged ≥ 18 years with an inadequate response to nasal corticosteroids.[2] In animal reproduction studies on cynomolgus monkeys (*Macaca fascicularis*) no evidence of maternal toxicity, effects on male or female fertility, embryotoxicity, teratogenicity or defects on neonatal growth have been reported when omalizumab was administered subcutaneously at doses up to approximately 10 times the maximum recommended human dose.[3] An observational study of the use and safety of omalizumab during pregnancy (EXPECT) was a postmarketing commitment to the US Food and Drug Administration that compared the maternal and neonatal outcomes of people with asthma treated with omalizumab ($n = 250$) vs. conventional drugs ($n = 1153$) during pregnancy.[4] No statistically significant difference between the omalizumab and conventional treatment groups was found with regard to the prevalence of major congenital anomalies (8.1% vs. 8.9%), live births (99.1% vs. 99.3%) or premature births (15.0% vs. 11.3%).[4] The European Medicines Agency has asserted that omalizumab treatment might be considered for pregnant patients with antihistamine-refractory severe chronic urticaria (CU).[5] However, a careful evaluation of the benefit-to-risk ratio is mandatory in every case and should be discussed with the pregnant patient in detail, owing to the long half-life of omalizumab.[5]

Current international urticaria guidelines recommend that patients with CSU are started on a second-generation H1 antihistamine (sgAH), increasing the dose up to fourfold in nonresponders; omalizumab can then be added in high-dose antihistamine-refractory patients.[2] Guidelines suggest the same therapeutic approach for pregnant patients, with caution.[2] However, data on treatment choices and their safety during pregnancy, as well as the effects of omalizumab treatment in patients with CSU on conception, pregnancy outcomes and newborn growth, are limited to a few case reports and 1 clinical study that collected data via a 47-item questionnaire completed by patients with CU who became pregnant during their disease course.[6–13] This lack of evidence is also important as the prevalence of CSU is greater in young women than in men, with a point prevalence in CSU of 1.3% and 0.8%, respectively.[13] Furthermore, CSU is often severe in female patients.[13]

The aim of this multicentre retrospective study was to evaluate, in a routine clinical practice setting in Italy, the efficacy and safety of omalizumab in patients with severe CSU refractory to sgAHs, who either became pregnant during treatment or started the drug during pregnancy.

Materials and methods

The data of adult patients with CSU treated with omalizumab between January 2016 and March 2023 were retrospectively collected from 10 secondary dermatological centres in Italy. The diagnosis was established by expert dermatologists based on the patients' medical history and clinical symptoms, according to the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Association (EAACI/GA²LEN/EDF/WAO) guidelines.[14,15] As stated by the Italian Medicines Agency, omalizumab may be administered to patients with CSU who are refractory to sgAH treatment and who have an Urticaria Activity Score over 7 days (UAS7) of ≥ 16.[16] The drug dosage was 300 mg every 4 weeks. Assessment of CSU severity during treatment was based on a reduction in UAS7 score.

Women aged ≥ 18 years who were pregnant and receiving one or more doses of omalizumab at any time during pregnancy, or who were taking omalizumab at the time of conception or during the 8 weeks before conception (a window selected to reflect omalizumab's half-life of 26 days) were evaluated in this study. Characteristics collected for each patient included their age, duration of CSU, comorbidities, omalizumab exposure and previous CSU treatments, past pregnancies or history of miscarriages, pregnancy outcomes (births, stillbirths, spontaneous abortions and elective terminations), livebirth characteristics [full term (≥ 37 weeks) or premature (< 37 weeks)], infant birthweight, neonatal adverse events (AEs) and congenital anomalies. AEs and serious AEs were documented by an expert dermatologist at each centre.

Statistical analysis

Quantitative variables were summarized as mean (SD) and range, and qualitative variables by the absolute and relative frequency of each possible value. UAS7 values at different timepoints were compared by Student *t*-test or Wilcoxon signed-rank test when the conditions for the use of Student *t*-test were not met. Differences were considered to be statistically significant when $P < 0.05$. Prism version 8.0 (GraphPad Software, La Jolla, CA, USA) was used for all statistical analyses.

Results

In total, 1625 patients with CSU [761 men (46.8%) and 864 women (53.2%); mean age 42.18 (10.52) years] were treated with omalizumab during the study period. Of the 864 women, 29 pregnant patients (3.4%) were evaluated: 23 (79%) conceived a child while on treatment with omalizumab (group A) and 6 (21%) started omalizumab treatment during their pregnancy (group B).

In group A, the mean patient age was 32.83 (3.69) years (range 26–41) and patients had a mean disease duration of 36.87 (35.72) months (range 4–120). Hypothyroidism ($n = 3$; 13%), asthma ($n = 2$; 9%), alopecia areata ($n = 2$; 9%) and coeliac disease ($n = 1$; 4%) were the main reported comorbidities. All patients in group A had previously been treated with sgAHs: 14 (61%) had a history of treatment with systemic corticosteroids (SCS) and 4 (17%) with ciclosporin. Seventeen patients (74%) reported previous normal pregnancies and healthy offspring. On average, conception occurred (as reported by patients) at 21.35 (32.38) weeks (range 2–156) of omalizumab treatment. At the time of conception, 17 patients (74%) were also taking sgAHs. After

discovering their pregnancy, 15 (65%) patients discontinued immediately both omalizumab and sgAH therapy; for CSU recurrence after omalizumab discontinuation, 3 (13%) restarted with sgAHs only and 4 (17%) with systemic prednisone, with variable dosages and schedules. Conversely, eight patients (35%) were exposed to omalizumab during the entire pregnancy. The median duration of pregnancy exposure to omalizumab was 34 weeks (range 6–37). Mean UAS7 score was 30.48 (4.72) before omalizumab treatment and was significantly reduced to 4.72 (6.97) at the time of omalizumab discontinuation owing to pregnancy ($P < 0.001$). Among patients in group A, we observed 23 births, including 21 liveborn singletons, 1 liveborn twin pair and 1 miscarriage. Among the livebirths, 22 were full-term and 1 was premature (moderately preterm at 32 weeks' gestation). Mean birthweight was 3.19 (1.22) kg. No congenital anomalies were reported. The premature baby appeared to go on to develop as per term-born babies.

After delivery, 11 patients (48%) resumed therapy with omalizumab and sgAHs, and 2 (9%) continued therapy with sgAHs. The remaining 10 (43%) reported clinical remission.

In group B, mean patient age was 36.67 (4.41) years (range 33–45) with a mean duration of CSU of 964.33 (48.47) months (range 2–120). Asthma, Hashimoto thyroiditis and multiple sclerosis were reported by two (33%), one (17%) and one (17%) patients, respectively. Also in this group, all patients had previously undergone treatment with sgAHs and half ($n = 3$) with SCS. Omalizumab was introduced at a mean of 10.83 (3.60) weeks' gestation and all patients were exposed to it until the end of pregnancy. In three patients (50%) omalizumab was added to sgAH therapy. The mean UAS7 score was 31.00 (0.89) before omalizumab treatment and was significantly reduced to 3.67 (1.37) at the time of omalizumab discontinuation in conjunction with childbirth ($P < 0.005$). There were seven liveborn infants in group B (five singletons and one twin pair). They all were full-term infants, with a mean birthweight of 3.24 (0.98) kg. No complications or congenital anomalies were recorded. No patient restarted omalizumab after delivery. In fact, CSU relapse was observed in three patients and was manageable with sgAHs.

Discussion

Managing a pregnant patient with CU is often a challenge for treating physicians. Recently, data from the PREG-CU study have shown that most pregnant patients with CU need to treat their urticaria, that sgAHs are the most used medication, and that rates of preterm births and medical problems of newborns are similar to those of the normal population and not linked to treatment used during pregnancy.[17–20] Omalizumab is classified as a category B medication during pregnancy (no risk in animal studies: no adequate studies in humans, but animal studies have not demonstrated a risk to the fetus).[16] Currently, the literature regarding omalizumab efficacy and safety in pregnant women is scant.[6–13] This study retrospectively analysed data from women who initiated omalizumab therapy during pregnancy, or who took the drug at the time of conception and continued therapy throughout pregnancy. Based on our data, no evidence of a relationship between omalizumab exposure and increased risk of AEs, pregnancy-related AEs or of AEs in newborns was found. These results are in line with those of the EXPECT study in patients with asthma treated with omalizumab.[4] Notably, in the EXPECT study, premature birth was identified in 15.0% of omalizumab exposed infants and 11.3% of the non-omalizumab-exposed comparator cohort.[4] In another retrospective study of 16 patients who used omalizumab to treat CSU during pregnancy, 4 had a preterm birth and 2 of them used SCS along with omalizumab.[13] This effect might be linked to SCS use, which has been associated with an increased risk of preterm birth.[13] Conversely, in our cohort of patients only 1 of 29 births (3%) was preterm. Furthermore, omalizumab proved effective in patients exposed from conception and throughout pregnancy, as well as in patients who started it after the second and third trimester (after the organogenesis period). Therefore, in our experience, there is no apparent increased risk of adverse outcomes in pregnant patients treated with omalizumab.

CSU may improve, remain unchanged or worsen during pregnancy. [4] The use of omalizumab to treat CSU before and during pregnancy does not seem to negatively affect maternal or fetal outcomes. The lack of published real-life data prohibited the ability to draw any firm conclusions about risks associated with its use. Future studies should be prospective and include as controls comparable women who have similar disease severity, without exposure to omalizumab.

Funding sources

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

C.P. has received consulting fees from AbbVie, Eli Lilly, LEO Pharma, Pfizer, Sanofi and Pierre Fabre; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Eli Lilly, LEO Pharma, Pfizer, Sanofi, Novartis and Pierre Fabre. C.F. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Almirall, LEO Pharma, Lilly, Novartis and Sanofi. A.B. has served as a speaker and/or consultant for AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Novartis and UCB. M.N. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, AbbVie, LEO Pharma, Eli Lilly and Amgen, outside the submitted work. The other authors declare no conflicts of interest.

Data availability

The data are all provided in the manuscript.

Ethics statement

This study was exempt from Institutional Review Board approval.

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