### **Case Report**

# Successful Treatment of Generalized Pustular Psoriasis during Pregnancy by Cyclosporin and Etanercept: Own Experience and Review of Literature

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### **Abstract**

Psoriasis is a common inflammatory skin disease affecting about 2% of the population. Generalized pustular psoriasis (GPP) is a rare variant of this disease, and it can be life-threatening for a pregnant woman and fetus.

Medication during pregnancy can be challenging since many drugs can cause marked adverse effects for a fetus or newborn baby. Because controlled studies are difficult to perform, the knowledge grows slowly, e.g., from case reports.

Here we describe a review of past and present treatments for GPP patients with a special reference to pregnancy and our experience on two GPP cases treated with cyclosporin and etanercept during pregnancy with successful outcomes of infants.

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**Submitted:** February 05, 2024 **Approved:** February 26, 2024 **Published:** February 27, 2024

**How to cite this article:** Harvima RJ, Harvima IT. Successful Treatment of Generalized Pustular Psoriasis during Pregnancy by Cyclosporin and Etanercept: Own Experience and Review of Literature. Ann Dermatol Res. 2024; 8: 007-011.

DOI: 10.29328/journal.adr.1001032

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**Keywords:** Generalized pustular psoriasis; Pregnancy; Treatment

Abbreviations: GPP: Generalized Pustular Psoriasis; PrGPP: Pregnancy-Related GPP; MTX: Methotrexate; CsA: Cyclosporin (A)



### Introduction

## Literature review of past and present treatments for pustular psoriasis

Psoriasis is a common skin disease affecting about 2% of the population. The etiology is multifactorial, including genetic and environmental background. Also, strong psychosocial stress seems to worsen the clinical picture [1].

The treatments of psoriasis vulgaris include topical emollients, corticosteroids of various strengths, and vitamin D and its analogs. Also, peroral methotrexate (MTX), cyclosporin (CsA), acitretin and fumarates are used. The newer oral apremilast, JAK blocker, and a variety of intravenous or subcutaneously injected biologics targeting TNF-alpha, IL-12, IL-23, and IL-17 have been developed for the treatment of psoriasis during the past two decades.

Pustular psoriasis is divided into 5 subgroups: 1) acute generalized (von Zumbusch variant), 2) generalized pregnancy-related (PrGPP), 3) circular (circinata), 4) infantile and juvenile, and 5) local pustular variant (palmoplantar pustulosis and acrodermatitis continua Hallopeau not

included) [2]. Pustular psoriasis is about 1.26 to 2 times more common in women than men [3-5].

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Decades ago, the use of systemic or strong topical steroids was recommended [6], although both treatment ways have been reported to even worsen pustular psoriasis [3,7,8]. Also, stopping high-dose corticosteroids can lead to exacerbation of GPP [3,9]. In a study of 155 patients with 34 fatal cases, death was concluded to relate directly to the use of steroids in 7 patients and the use of MTX in 2 patients. Eight other patients died of uncontrollable pustular psoriasis during steroid treatment. A very careful consideration was suggested for the use of steroids or MTX in pustular psoriasis [9].

Two GPP patients got a good response at 2.5-5 mg/kg of CsA [10], which has given a good response also in the treatment PrGPP [11,12].

Treatment of psoriasis arthropathica by MTX leads to hepatitis and liver fibrosis. Stopping the drug caused the development of pustular psoriasis. CsA at 12 mg/kg was effective but toxic to kidneys. Reducing the dose to 5 mg/kg and combining it with topical steroids the response was



obtained gradually in 4 months, and the dose reduced to 4 mg/kg kept all joint and skin symptoms away for 9 months of follow-up [13].

Stopping MTX for psoriasis caused exacerbation of severe GPP, and medication was continued by CsA at a dose of 7.5 mg/kg giving a great response in 3 days. However, the effect on psoriatic plaques was partial after 1 month but was complete after 5 months at a dose of 3.5 mg/kg [14].

For a patient with severe GPP and simultaneous acrodermatitis continua Hallopeau [15], the only effective treatment was prednisone 50 mg/day. Reducing the dose led to relapse. Using CsA at 8 mg/kg and 7.5 to 10 mg/kg prednisone a clear response was obtained in 3 weeks.

At the time of our cases in the 1990s, there were no generally accepted guidelines or medications for pustular psoriasis. For GPP treatments, there have been later established as  $1^{\rm st}$  line treatments acitretin, CsA, MTX, and infliximab; and as  $2^{\rm nd}$  line adalimumab, etanercept, PUVA in combination with topical steroids and calcipotriol and topical tacrolimus [16,17]. Also, here is now available the recently FDA-approved IL-36 inhibitor spesolimab for GPP.

About 1% of subjects with plaque psoriasis can develop generalized pustular psoriasis (GPP) [8] that can be lifethreatening, including also for a pregnant woman and fetus [18,19], with a mortality rate of 2% - 16% [2]. PrGPP is rare and appears typically during the 3rd semester of pregnancy [20]. According to the Textbook of Dermatology, only fewer than 200 cases have been confirmed in the world [6] and this number also includes impetigo herpetiformis, which is considered a separate disease by some authors [5,21-23].

PrGPP cases have been rarely described during 1968-1997, that is, only 6 cases [3,4,24], of which only 2 cases were during 1983-1999. Less than 4% (4/104 and 1/28, i.e., a total of 5/132) of all described cases of pustular psoriasis have been pregnancy-related [3,24].

Placenta dysfunction is linked to impetigo herpetiformis [21] and in one case the fetus died at the 33rd week of gestation at 80 mg/day steroid treatment [23]. Impetigo herpetiformis during the first trimester led to stillbirth [25].

Here we describe our experience as two case reports [26,27] about successful outcomes by use of CsA and etanercept during pregnancy in patients with GPP.

## Case reports

### Case 1 describes pregnancy-related GPP [26]

A 37-year-old suffering from mild psoriasis vulgaris treated only by topical moderate strength corticosteroids during her  $2^{nd}$  pregnancy at  $35^{th}$  week of gestation GPP within a week. Antihistamines moderate to high potency steroids

and calcipotriol with UVB treatment did not give a response, so CsA 2.5 mg/kg/day was started. In 3 days the formation of pustules ended with a simultaneous decrease of itch. In a few days, the pustules started to go down. There was no effect on kidney function or blood pressure. However, liver function value ALAT increased from 20 to 94 U/L so CsA was reduced to 1.25 mg/kg/day. SR was elevated 94-97 mm/h. One week later Alat value still increased to 116 U/L. The condition was considered pregnancy hepatosis and artificial birth was initiated. The baby got Apgar 9/10 and further growth developed normally up to 2 years of follow-up. After birth, the liver function normalized rapidly in 2 days, but alkaline phosphatase was elevated at 548 U/L for 2 months. Due to the increase of palmar pustules, CsA was increased to 5 mg/kg/ day for 2 weeks and then reduced to 3,75 mg/kg/day, with topical steroids with a great response, and later slowly in 5 months, with earlier mild psoriasis vulgaris lesions as followed for 2 years.

### Case 2 describes two sisters with GPP [27]

Younger sister developed plaque psoriasis at the age of 2 that developed to pustular type 3 years later. The treatments included acitretin, CsA, MTX, and oral and topical corticosteroids and phototherapies SUP, UVB, and PUVA until arthropathic GPP developed at age 31.

Etanercept was administered successfully at 25 mg twice a week for 2 years until the 31st week of gestation since at that time there was no sufficient data on its safe use in pregnancy. After cessation of etanercept, GPP developed rapidly, and the delivery was induced 5 weeks later. A healthy boy was born growing normally followed up to 9 years of age. The patient's GPP was re-treated with etanercept and 20 mg/week MTX giving a good response in 4 weeks, and 5 months later MTX was reduced to 10 mg/week also with sufficient effect on joint symptoms.

The older sister had plaque psoriasis from effect on age 10. Pustular psoriasis developed at age 21, and topical steroids and acitretin gave a good response for years, until at the age of 28, PP developed. CsA at 150 mg/day gave a good response for 9 months, until a relapse which was treated by 300 mg/day CsA and 25 mg/day prednisolone for about a week, and GPP was confirmed to have developed to von Zumbusch type with life-threatening condition. Infliximab infusion of 400 mg (5 mg/kg) gave a dramatic response within hours. After a few routine infliximab infusions, the treatment for practical reasons due to long travel to the hospital was changed to etanercept 25 mg twice a week, which was modified to 50 mg once a week 3 years later used for an additional 13 years with a few pustules occasionally in palmar and axillar areas treated with topical treatments with steroids and calcipotriol.

After about 7 years of etanercept, she wanted to get pregnant. After getting data from the files of the drug company with about 140 successful pregnancies without any marked adverse side effects, we decided to show her the green light. A



healthy boy was born growing normally followed up to 7 years of age. At the age of 3, mild atopic dermatitis and asthma were diagnosed.

## **Discussion**

There are many drugs with variable efficiency used for decades for psoriasis, like MTX and acithretin. However, both cannot be used during pregnancy. Also, there is at least partially limited data on biologics to be safe in pregnancy, thus not recommended for use. The knowledge of drugs suitable to be used during pregnancy will grow slowly starting from case reports and inadvertent challenging of drugs in clinical studies and from cases in clinical practice.

Our pregnancy-related GPP in 1998 was extremely rare and was the first and only one we have seen also since then, and was treated effectively by CsA [26] which was not reported earlier. Thereafter, reports have been published with success and with a healthy infant [18,28]. We selected CsA because there were concerns about the possible adverse events by systemic steroids.

According to the literature, GPP patient is expected to get marked relief soon after birth-giving [6]. This was also the case in our patient, though reducing the CsA dose caused a slight relapse, and the dose increase was helpful, in later months dose was gradually decreased and finally stopped.

CsA is transferred from the placenta into the cord blood of the fetus. The ratio of CsA in cord blood/mother plasma is 0.63, and CsA concentrations in the amniotic fluid are 234 ng/ml and cord blood 57 ng/ml after 8 hours of CsA dose of 325 mg [29].

CsA is secreted into breast milk, with a ratio of milk/plasma of 0.17-0.40 [30,31]. Breast milk CsA concentration has been reported to be at the level of 101-263 ng/ml [32]. In a case [33] where CsA concentration was in the mother's blood 260 ng/ml, in breast milk on average 596 ng/ml, and simultaneously in infant blood less than 3 ng/ml (< 1/60): the child was grown normally during 2 years of follow up.

There are concerns about whether breastfeeding should be avoided due to the immunosuppressive effect of CsA as by the American Academy of Pediatrics, Committee on Drugs in 1994 [34]. However, wide experience in transplant patients with immunosuppressive organ-rejection medication has given results indicative that during pregnancy the CsA is safe [35,36] and the challenge for the fetus is higher per time and weight than after birth in breast-feeding time possibly for a few months when the baby is also getting more weight. By estimating mother milk to contain 600 ng/ml CsA, and the baby taking 500 ml of breast milk/day, then the CsA dose for the baby is about 300  $\mu g$ , i.e., about less than 0.07 mg/kg/day, which is far below the therapeutic level of about 2 to 5 mg/kg/day. Our patient [26] wanted to breastfeed her baby for

4 months, and the baby was grown normally during a 2-year follow-up.

A recent case of PrGPP was treated by topical steroids and oral prednisolone at 0.5 mg/kg [37], suggesting an individual variation in response even for low- to medium-dose steroids.

Our older sister patient with the von Zumbusch variant of GPP experiencing a life-threatening situation survived by use of infliximab suggested to be used as 1<sup>st</sup> line treatment giving a very fast response within a few hours [27]. Similarly, PrGPP was treated post-partum with infliximab as a case report [38]. There is a case report of fatal cases of 10 mg/kg by 8-week intervals infliximab use for Chrohn'n disease during pregnancy [39]. The baby was healthy until 3 months of age when got a BCG vaccination and died 1.5 months later for disseminated BCG; thus, BCG vaccination is recommended at a much later time for the baby.

Certolizumab and the newer spesolimab can be used during pregnancy but so far there are no reports about PrGPP treated with these drugs. Also, by the presentation of Murase [40], spesolimab is conditionally recommended in GPP, if CsA cannot be used. In our later cases [27], etanercept was effectively used during pregnancy in both sisters of GPP without any later adverse effects for the babies followed up to 7 to 9 years. Also, as presented recently [40], TNF-alpha inhibitors etanercept, adalimumab, and infliximab are conditionally recommended during pregnancy and lactation. Recently published cases are giving positive signals for medication during pregnancy by secukinumab [41] and 2 cases by ixekizumab [42].

### Conclusion

- CsA is effective and safe in pregnancy-related GPP and during the course and lactation at least in this patient case.
- 2. Etanercept was used successfully and safely during pregnancy in two GPP patients.
- In the future, more experience and safety data are expected to be available with regard to infliximab, adalimumab, secukinumab, and especially to certolizumab and the new spesolimab used during pregnancy and in GPP.

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