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Anakinra Use During Pregnancy in Patients with Cryopyrin-Associated Periodic Syndromes (CAPS)

Zenas Chang, MD, MS[1], **Catherine Spong, MD**[1], **Adriana A. Jesus, MD, PhD**[2], **Michael Davis, NP**[2], **Nicole Plass, RN**[2], **Deborah L. Stone, MD**[3], **Dawn Chapelle, CPNP**[2], **Patrycja Hoffmann, NP**[3], **Daniel L. Kastner, MD, PhD**[3], **Karyl Barron, MD**[4], **Raphaela T. Goldbach-Mansky, MD, MHS**[2], and **Pamela Stratton, MD**[1]

[1]Eunice Kennedy Shriver National Institute of Child Health and Human Development

[2]Translational Autoinflammatory Disease Section, NIAMS, NIH

[3]Inflammatory Disease Section, Medical Genetics Branch, NHGRI, NIH

[4]Division of Intramural Research, NIAID, NIH

Abstract

Objective—To describe the pregnancy course and outcome, and use of anakinra, a recombinant selective IL-1 receptor blocker, during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS), including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multi-system inflammatory disease (NOMID).

Methods—Women currently enrolled in natural history protocols (NCT00059748, and/or NCT00069329 under IND) who have been pregnant were included. Subjects underwent a structured, standardized interview with regards to maternal health, pregnancy and fetal outcomes. Medical records were reviewed.

Results—Nine women (four with FCAS, one with MWS and four with NOMID) reported one to four pregnancies, each resulting in a total of fifteen FCAS, three MWS, and six NOMID pregnancies. Six births from FCAS mothers and three births from NOMID mothers occurred while patients were receiving anakinra. If a woman became pregnant while taking anakinra, the pre-pregnancy anakinra dose was continued. Anakinra dose was increased during one twin pregnancy. No preterm births or serious complications of pregnancy were observed. One fetus of the twin pregnancy had renal agenesis and suffered fetal demise. Genetic testing showed the deceased twin carried the same *NLRP3* c.785T>C, p.V262A mutation as the mother. The other twin is healthy and mutation negative.

Conclusions—Anakinra was continued during pregnancy in women with CAPS and provided significant, persistent CAPS symptom relief while continuing to prevent the long-term sequelae of CAPS. Anakinra was well tolerated. Although a causal relation between anakinra and renal agenesis seems unlikely, further safety data are needed.

Corresponding Author: Raphaela Goldbach-Mansky, MD, MHS, Translational Autoinflammatory Disease Section, NIAMS, NIH, Bldg 10, room 6D47B, 10Center Dr., Bethesda, MD 20892, USA, goldbacr@mail.nih.gov, Phone: +301-435-6243.

Introduction

Cryopyrin-associated periodic syndromes (CAPS) is a monogenic auto-inflammatory syndrome that includes the disease spectrum of familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multi-system inflammatory disease (NOMID or CINCA in Europe)[1] with an estimated incidence of 1 in 360,000[2]. CAPS is caused by missense, gain of function mutations in *NLRP3*. In 60% of clinically-identified NOMID patients, mutations occur as *de novo* germline mutations[3–6], and two-thirds of the Sanger sequencing mutation-negative patients have somatic mosaicism[7], which lead to immune dysegulation due to increased IL-1β activation and secretion. Untreated CAPS patients present with markedly elevated erythrocyte sedimentation rate and C-reactive protein levels and a mild hypochromic microcytic anemia resistant to iron supplementation[3,5,8]. Affected patients also present with multiple organ systems involvement. Inflammatory disease features begin in infancy with neutrophilic urticaria-like rashes and fevers. Nondestructive arthralgia and arthritis are common. Epiphyseal bony overgrowth is seen in about 50% of NOMID patients. In MWS/NOMID overlap and NOMID, chronic aseptic meningitis often causes increased intracranial pressure (ICP) leading to headaches, early morning vomiting, and cognitive dysfunction. Chronic increased ICPs can lead to optic nerve atrophy and vision loss[8]. Death before reproductive age is reported in almost 20% of severely-affected patients that are untreated with IL-1 blocking agents[8].

Anti-inflammatory and immunosuppressive medications used to treat arthritis and other autoimmune diseases have limited efficacy; whereas, IL-1 receptor blockade prevents skin manifestations, decreases CNS inflammation and intracranial pressure, and greatly reduces musculoskeletal pain and damage. Anakinra, a recombinant selective IL-1 receptor blocker, has a half-life of 4–6 hours and requires daily dosing[5]. By targeting IL-1 signaling, significant relief of clinical symptoms is seen, and other immunosuppressive drugs are not needed. Although IL-1 blockade will not reverse visual and auditory damage that occurred prior to treatment, treatment can prevent progression of organ damage[9].

Given the increased quality and longevity of life while on anakinra, a pregnancy category B agent, female CAPS patients are considering childbearing. Several CAPS patients have had successful pregnancies prior to using anakinra. Once anakinra is started, continuation during pregnancy may be beneficial to the mother but has unknown effects on the pregnancy, fetus and newborn. A review of pregnant patients with CAPS taking and not taking anakinra may provide insights into the pregnancy course, the effects on the fetus, and newborn outcomes.

Methods

Patients were enrolled in natural history protocols NCT00059748, and/or NCT00069329 under previous IND and provided information on their pregnancy course and neonatal outcome. For this review, pregnancies were included regardless of whether the woman took anakinra.

All patients underwent a structured telephone interview. Standardized questions addressed symptoms prior to and after starting anakinra, number of total pregnancies, outcomes of pregnancies, maternal health on anakinra (if applicable), pregnancy course, neonatal issues and complications.

Results

Women were diagnosed with FCAS, MWS/NOMID and NOMID at varying ages and started on anakinra (Table 1). Manifestations of CAPS reported by every patient (9 out of 9) included headache, fever, rash, and arthralgia (supplementary Table 1), which were controlled with anakinra (starting dose of 100 mg). Higher dosing was required to obtain symptom relief for MWS or NOMID patients, some of whom experienced irreversible hearing (5 of 5) and vision (3 of 5) loss prior to anakinra use. Pre-pregnancy anakinra dosage was continued in all but one patient who had a twin gestation. Her anakinra dose was increased to account for maternal weight gain.

Whether anakinra was used during pregnancy, pregnancy outcomes, and number of infants born with or without CAPS are presented in Table 2. Patient descriptions are presented in supplementary Table 2. Pregnancy course, anakinra use and neonatal outcomes are presented in Table 3. Of the 24 pregnancies reported, five ended in miscarriage and one in ectopic pregnancy. Four of five miscarriages occurred during pregnancies where women were not taking anakinra. Thus, the miscarriage rate was 30% for pregnancies not on anakinra versus 10% for pregnancies on anakinra. For the other pregnancies, nine occurred prior to anakinra use and nine occurred while taking anakinra. One fetus died of renal agenesis, but the others (n=18) were all born at term. Three women underwent cesarean section (two on anakinra, one not), and no adverse newborn outcomes were observed. While taking anakinra, only one patient with twins was induced for preeclampsia superimposed on chronic hypertension, but otherwise no one had any pregnancy complications.

Genetic testing of the fetal demise showed that the fetus and mother carried the same *NLRP3* c.785T>C, p.V262A mutation. The live-born twin was mutation negative and healthy. Of the 18 live born infants, 8 were mutation positive; two infants had NOMID, two MWS, and four were affected by FCAS. Four neonates were observed in the NICU, and one of these received IV antibiotics for an elevated white blood cell count. One infant with NOMID first manifested joint swelling at thirteen months of age. A neonate with MWS developed facial urticaria within the first month of life. Other than renal agenesis, no birth defects were noted. Mutation-positive infants were often genetically tested early in life and initiated IL-1 blocking therapy between 8 and 17 months of age.

Discussion

CAPS is a spectrum of rare inherited, monogenic, autoinflammatory syndromes characterized by constitutive IL-1 overproduction and secretion causing distinct clinical and inflammatory symptoms. If untreated significant end-organ damage develops. On treatment with IL-1 blocking agents, symptoms are mild or completely resolve. In this cohort, anakinra was continued during pregnancy and breastfeeding in 9 of 18 term pregnancies of

mothers who had CAPS. Overall, symptoms did not worsen during pregnancy nor were there significant adverse pregnancy or neonatal outcomes.

In general, over two-thirds of NOMID patients who start therapy late in life remain below the third percentile for height. On anakinra treatment catch-up growth is often seen such that patients treated early in life often achieve normal height and weight ([9] and unpublished data). Dosing is adjusted to levels that provide symptomatic relief, normalization of acute phase reactants and no evidence of organ inflammation. Our preliminary approach suggests that, dosage adjustment during pregnancy is necessary only if pregnancy weight gain exceeds 10–12 kg. CAPS symptoms worsened after one woman gained 19 kg during the first 20 weeks of a twin pregnancy. Symptoms resolved after increasing the dose.

The symptoms of a CAPS flare, more frequent headaches, visual disturbances and joint pain, are also common symptoms in pregnancy and may not be easily distinguished. An evaluation including CBC, ESR, and CRP may help to differentiate. ESR has a two-fold increase from 18–48 mm/h in the first half to 30–70 mm/h in the second half of pregnancy[10]. Maternal CRP may increase early in gestation from a median of 1.495 to 3.68 mg/l[11]. By comparison, the increases in CRP in a CAPS flare are often much higher. If differentiating between a flare and pregnancy complication remains equivocal, a lumbar puncture may be useful to look for aseptic meningitis or increased intracranial pressures in women with headaches.

A report of 100 mg/day of anakinra use throughout pregnancy is published in a woman with adult onset Still's disease. Her symptoms fully resolved after starting anakinra. The term infant was severely growth restricted but otherwise healthy[12].

Despite the case of renal agenesis, there are no reports suggesting elevated IL-1 levels or IL-1 blockade is associated with organ malformation; however, the deceased fetus carried the same *NLRP3* mutation as the mother. Single umbilical arteries are associated with renal agenesis[13], and umbilical cord abnormalities were reported in 30% of NOMID babies[8]; however, no umbilical cord abnormalities were noted in the twin pregnancy. The patient had a family history of diabetes and twin pregnancy, which are factors associated with renal anomalies[14]. Renal agenesis has not been previously reported with CAPS mutations. Systematically recording pregnancy outcomes in mothers with *NLRP3* mutations, and genetic screening for de-novo *NLRP3* mutations in patients with renal agenesis would answer whether this is a CAPS-related anomaly. Gestational diabetes and preeclampsia, both common pregnancy complications, each occurred in a single pregnancy.

Case series of pregnancy and newborn outcome for affected infants have been reported. Prieur et al's 1987 description included 30 NOMID-affected mothers and 20 NOMID-affected children. Preterm birth (n=11), polyhydramnios (n=2), omphalocele (n=3), respiratory distress (n=3) and icterus (n=5) were reported[8]. About 50% of NOMID-affected infants were small for gestational age (SGA), and had late closure of fontanelles[8,15], fetal and neonatal effects possibly attributed to the disease. In this study, birth weight and height did not differ significantly between progeny with or without CAPS mutations and was similar to that of the general population.. Improved prenatal care with

increased monitoring may result in a decreased risk of SGA; in addition, most births included prior to anakinra treatment were to women with less severe disease than those in previous reports which likely accounts for the lower complication rate.

Inflammatory cytokines including IL-1 may play a role in miscarriage, initiation of labor and rupture of membranes in the setting of infection[16]. While the miscarriage rate was higher among those not taking than those taking anakinra (30% versus 10%), the rates are similar to the miscarriage rate in the general population (20%). Whether this higher rate was due to IL-1-induced inflammation, the occurrence of more CAPS-affected progeny or chance is not known. No preterm births and several instances of spontaneous rupture of membranes (SROM) at term occurred both among those taking and not taking anakinra. While the small sample size limits an association between CAPS and spontaneous rupture of membranes or miscarriage, the occurrence is of interest. It is reassuring that no preterm births occurred in these women.

Systematic collection of pregnancy and newborn outcome data on new drugs taken during pregnancy and with breastfeeding is important[17,18]. Given the low incidence of CAPS, it is not possible to conduct a clinical trial of anakinra prescribed in pregnancy with sufficient power to assess safety or efficacy. While CAPS is studied as part of a natural history protocol, few women became pregnant and only recently have they been taking anakinra. Furthermore, the safety assessment is complicated by physiologic changes in pregnancy, which are not well-characterized in unusual diseases. Inflammatory markers were not measured in all women nor were anakinra levels measured in any. While the study team and Gynecology Consult Service worked closely together to assess and provide management guidelines for pregnant women, these women received care in the community. Our tabulation of their pregnancy and neonatal outcomes are a retrospective review supplemented by structured interviews, detailed notes and their obstetric record, where possible.

In summary given significant mitigation of CAPS symptoms while on anakinra, treatment was continued throughout several pregnancies based on clinical judgment. There does not appear to be a significant detriment to maternal or pediatric health by continuing anakinra. Potential increases in dosing, possible organ agenesis, and breastfeeding should be discussed, as anakinra has been shown to pass through the placenta and enter breast milk[17]. Titration of dosage may be required based on symptoms. Pharmacokinetic studies during pregnancy may be helpful in determining the optimal dosage, as pregnancy is associated with increases in blood volume and weight and may alter drug metabolism. Given the autosomal dominant nature of these syndromes, genetic counseling regarding the risk of affected offspring should be offered. This is a first report of pregnancy outcomes in CAPS patients of which 50% of pregnancies occurred while the women were taking anakinra. More data on pregnancy outcomes will help to consider the risks and benefits of using anakinra in pregnancy and breastfeeding in CAPS disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics

Patient	Diagnosis	Mutation	Age at Diagnosis	Age started anakinra	Gravida	Term pregnancies on anakinra (n)	daily dose (mg)
1	FCAS	L353P	37	37	4	0	100
2	FCAS	L353P	25	25	3	2	100
3	FCAS	L353P	28	28	4	1	100
4	FCAS	F523C	22	22	4	3	100
5	MWS/NOMID	D303N	46	46	3	0	400
6	NOMID	D303N	27	27	1	0	600
7	NOMID	L264F	5	18	1	1	300
8	NOMID	V262A	9	11.5	1	1	239, then 300*
9	MWS/NOMID	D303N	25	25	3	1	100

Patients with CAPS were diagnosed at varying stages of life. No patient already on anakinra stopped taking the medication while pregnant. Mutations listed are in the CIAS-1 gene.

*Dose adjustment increase during pregnancy

Table 2

Pregnancy Outcomes

Patient Mother	Diagnosis	Total number of Pregnancies	Number of Pregnancies on Anakinra	Number of Pregnancies not on anakinra	Number of Miscarriages, demises** or Ectopic Pregnancies*	Total Live Births on or off anakinra	Number of live births prior to Anakinra	Number of live births while on Anakinra	Number with Mutation	Child's Diagnosis
1	FCAS	4	0	4	2* (off anakinra)	2	2	0	0	N/A
2	FCAS	3	2	1	0	3	1	2	1	FCAS
3	FCAS	4	1	3	0	4	3	1	2	FCAS x2
4	FCAS	4	3	1	1 (on anakinra)	3	0	3	1	FCAS
5	MWS/NOMID	3	0	3	2 (off anakinra)	1	1	0	1	MWS/NOMID
6	NOMID	1	0	1	0	1	1	0	1	MWS/NOMID
7	NOMID	1	1	0	0	1	0	1	0	N/A
8	NOMID	1 (twin gestation)	1	0	1** (fetal demise, on anakinra)	1	0	1	1 (fetal demise)	NOMID
9	MWS/NOMID	3	1	2	1 (off anakinra)	2	1	1	2	MWS x2
		24	9	15	7	18	9	9	9	

* one ectopic and one miscarriage

** fetal demise of one fetus with renal agenesis at 30 weeks in twin dichorionic-diamniotic pregnancy

Table 3

Pregnancy course and neonatal outcomes of term pregnancies on anakinra

Maternal health and pregnancy course									
Patient pregnancy*	**Maternal Age at Pregnancy**	**Dose mg**	**Other medications**	**Symptoms During Pregnancy**	**Preterm labor**	**Preeclampsia or hypertension**	**Gestational Diabetes**	**Abnormal Placentation**	**Umbilical Anomalies**
2b	26	100	PNV**	None	None	None	None	None	None
2c	28	100	PNV	None	None	None	None	None	None
3d	35	100	PNV	None	None	None	None	None	None
4b	24	100	PNV	None	None	None	None	None	None
4c	25	100	PNV	None	None	None	None	None	None
4d	26	100	PNV	None	None	None	None	None	None
7a	28	300	PNV	headache	None	Only Chronic hypertension	None	None	None
8a	19	239 to 300	PNV	headache, joint pain	None	none	None	None	None
9b	27	100	PNV	leg swelling	None	None	None	None	None

Neonatal outcomes									
	Birth Weight	**Birth Height (in)**	**Delivery Age (wks)**	**Mode of delivery**	**Diagnosis**	**Symptoms**	**Initiation of Anakinra treatment**	**Onset**	**Breastfeed**
2b	8lb 4oz	20	41	Vaginal	N/A***	N/A	N/A	N/A	No
2c	8lb	19.5	41	Vaginal	FCAS	Rash	17mo	Birth	No
3d	7lb 8 oz	22	38	Vaginal	FCAS	Rash	8mo	Birth	3 months
4b	7lb 10oz	21.5	37	Vaginal	N/A	N/A	N/A	N/A	No
4c	6lb 9oz	20.5	37.5	Vaginal	FCAS	Rash	15mo	Birth	No
4d	7lb 6oz	21.5	39	Vaginal	N/A	N/A	N/A	N/A	No
7a	9lb 2 oz	21	40	Cesarean section	N/A	N/A	N/A	N/A	1 year w/solids
8a	5lb 13oz	U****	38.7	Vaginal	N/A	N/A	N/A	N/A	<1 month
9b	7lb 12oz	20	“Term”	Cesarean section	MW	Rash	8mo	1st month	No

* first pregnancy is indicated by a, second pregnancy by b, etc.

** PNV is Prenatal Vitamins

*** N/A is not applicable (*NLRP3* mutation negative)

**** U is unknown