International Multi-Centre Study of Pregnancy Outcomes with Interleukin-1 Inhibitors

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ABSTRACT

Objective. **To address the lack of outcome data concerning pregnancies exposed to the interleukin-1 (IL-1) inhibitors prior to conception in both men and women, during pregnancy and breast feeding.**

Methods. **Retrospective data were collected from members of the International Society for Systemic Autoinflammatory diseases and collated in a single center. A uniform data collection sheet was used to obtain standardized data including maternal age and diagnosis, type and duration and response to IL-1 blockade, and pregnancy duration, delivery, mode of feeding and neonatal development.**

Results. **There were 31 maternal-exposed pregnancies from seven countries and we report the first data on paternal exposure; six to anakinra and 5 to canakinumab, with no negative outcomes. We also report the first data on canakinumab exposed pregnancies; eight pregnancies which resulted in the delivery of 7 healthy infants of normal gestational age and birthweight. There were 23 anakinra-exposed pregnancies resulting in the birth of 21 healthy infants, and one baby with unilateral renal agenesis and ectopic neurohypophysis.**

There were two first trimester miscarriages affecting a mother with active disease. There were no serious neonatal infections. Fourteen infants were breast fed with no complications. There were no reports of developmental delay, with follow-up of up to 10 years (median 18 months).

Conclusion. **This series substantially increases the published experience of IL-1 blockade and reproduction including the first data on canakinumab and on paternal exposure to these**

agents. Data are generally reassuring, although the case of renal agenesis is the second reported in an anakinra-exposed pregnancy.

The first interleukin-1 inhibitor was licensed for use in rheumatoid arthritis in 2001, however, these agents have been most dramatically effective in the systemic autoinflammatory diseases (SAIDS)(1). These diseases generally present during childhood, (2) and with better disease recognition and diagnostics, their apparent incidence is rising and diagnostic delay is decreasing. Treatment with interleukin-1 (IL-1) antagonists completely controls symptoms in a number of SAIDS, with dramatic and sustained improvement in quality of life.(3) For patients with genetically determined SAIDS disease, these life-transforming therapies are likely to be required lifelong and many are unable to stop the medication prior to conception or during pregnancy.

More than a decade after the first reported use of IL-1 inhibition in SAIDS,(4) an increasing number of patients are reaching reproductive age and contemplating starting a family. For patients with well controlled disease and an expectation of a near normal duration and quality of life, information concerning their fertility and the potential risks to themselves and their children is of enormous importance. However, even compared to other biologic medications, few data on the safety of IL-1 antagonist are available in relation to conception, pregnancy or breast feeding. This paucity of sound evidence is recognized in a recent international consensus document on use of antirheumatic drugs around pregnancy (5) whilst this may reflect the rarity of SAIDS, the lack of data is compounded by exclusion of reproductively active subjects from drug trials, and by manufacturers discouraging the use of biologic agents in women contemplating pregnancy. As men must also use contraception when participating in drug trials, there is a total lack of published data on the health of offsprings born to fathers receiving IL-1 antagonists.

Currently there are three IL-1 antagonists, anakinra (Kineret®, Sobi), canakinumab (Ilaris®, Novartis) and rilonacept (ARCALYST®, Regeneron Pharmaceuticals) and their characteristics are summarized in Table 1.

To create a much needed evidence base to inform decision making for our patients, the international autoinflammatory community has come together to provide this data with suggested recommendations for managing conception and pregnancy in this group of patients on these medications.

PATIENTS AND METHODS

A request for data was made in 2012 to members of the International Society for Systemic Autoinflammatory diseases. A data collection sheet was used to obtain standardized retrospective data including maternal age, autoinflammatory syndrome diagnosis, obstetric history, type and duration of IL-1 blockade, biochemical and clinical response to IL-1 inhibition, pregnancy duration and delivery mode. Infant data for APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score, birth weight, congenital abnormalities, development, breast feeding status and age at last follow-up were collected. The study was approved by the Royal Free NHS Trust ethical committee, and consent was obtained by the treating physician and indicated on the data collection sheet. Paternal exposure data were collected by retrospective review of case notes.

RESULTS

We identified 43 pregnancies exposed to IL-1 inhibitors from seven countries, including 14 canakinumab-exposed pregnancies, of which 8 were maternal (Table 2) and 29 anakinra-exposed pregnancies of which 23 were maternal (Table 3). We report the first data on paternal exposure to anakinra (n=6) and canakinumab (n=5) (Table 4). We report the outcome of 14 neonates breast fed by mothers taking anakinra (n=10) or canakinumab (n=4) for up to ten months duration, with no reported serious infections (Tables 2 and 3). There were no developmental abnormalities with median follow-up of 18 months (range 1 week to 10 years). There were no cases of rilonacept use in pregnancy.

In keeping with the known favorable safety and efficacy profiles of these medications, there were no reported serious infections in the mothers nor neonates and disease was in complete clinical and biochemical remission in all but three cases (detailed below)

Canakinumab

Eight pregnancies, from seven women, were exposed to canakinumab and resulted in seven live births (Table 2). A single case of miscarriage occurred at six weeks to a 26-year-old mother with refractory Cogan Syndrome, with only a partial clinical and biochemical response to canakinumab at a dose of 150mg monthly. This was her second miscarriage, the first occurring on anakinra the previous year. Of the seven live births, mean maternal age was 24 years (range 16-32 years), all were in complete clinical and biochemical remission for CAPS (n=4), FMF (n=2), and one case of unexplained inflammatory illness. Pregnancies were uneventful, all reaching full term and normal birth weight; mean 3.58kg (range 3.3-4.48kg). Data on mode of delivery were available for five cases, with three cesarean sections and two vaginal deliveries.

Duration of treatment and its relation to pregnancy differed in each case; two babies were conceived on canakinumab which was discontinued as soon as pregnancy was confirmed in the 1st trimester, at 8 weeks and 12 weeks respectively. Two mothers switched to anakinra, at 8 and 36 weeks, and one was treated from before conception to term with 300mg canakinumab 8 weekly, with last dose at 36/40.

Five babies were born to three fathers who were on long term treatment (median 24 (Range 6-73) months) at time of conception for CAPS (n=2) and TRAPS (n=1). This included two fathers who had CAPS complicated by AA amyloidosis and prior to effective treatment with anti IL-1 agents (one each of anakinra and canakinumab) were confirmed infertile with severe oligospermia. 66% of the offspring were male (Table 4). At mean follow-up of 6.83 (range 4-10) years, no growth or developmental abnormalities have been identified.

Four babies were breast fed by mothers' prescribed regular canakinumab. There were no reported serious infections and no developmental abnormalities at a mean follow-up of 2.2 years (range 5 months to 4 years).

Anakinra

29 pregnancies were exposed to anakinra in total, 23 through maternal exposure, resulting in the births of 28 infants (Table 3). Mean maternal age was 29 years (range 20-38 years). Maternal diagnoses were CAPS (12), adult onset Still's Disease (AOSD) (4), FMF (3), TRAPS (2), pericarditis (1), and Cogan syndrome (1). All patients were in complete clinical and biochemical remission with exception of the 2 women with AOSD and Cogan syndrome, whose diseases were less well suppressed. 39% of mothers took anakinra continuously from before conception to delivery and during the puerperium. Three mothers conceived on anakinra but discontinued it when pregnancy was confirmed at up to 16/40. Three women started anakinra during pregnancy; two were switched to anakinra from canakinumab before 8/40, and one started at 22/40 due to active inflammatory disease. A single miscarriage occurred, at 12 weeks gestation in a 25-year-old

female with refractory Cogan syndrome; she had achieved only a partial clinical and biochemical response despite dose escalation of anakinra to 200mg daily, which she had taken before conception and throughout the first trimester.

A 29 year old female with AOSD, who had a history of two miscarriages at 10 and 13 weeks and an ectopic pregnancy, delivered a healthy girl at 38 weeks, having started anakinra 100mg before conception and continued it until 25/40.

There was no history of infection in either the mothers or babies exposed to anakinra. Where data were available regarding mode of delivery, seven (60%) babies were born via spontaneous normal delivery, four by cesarean section and two deliveries were induced at between 35+1 (for vaginal bleeding)- 41+1 weeks.

All babies were born healthy with normal APGAR scores at 10 minutes and 50% were male. There was a single case of ectopic neurohypophysis with growth hormone deficiency and left renal agenesis in a baby boy born to a mother aged 30 years with AOSD. It was the mother's first pregnancy and she had corticosteroid refractory disease at the time of conception. Anakinra therapy began at nine weeks gestation and continued until elective caesarean section at 38+1/40 with excellent clinical and biochemical response. The infant was developing normally at time of last contact aged 15 months.

Ten babies were breast fed by mothers taking anakinra for up to ten months with no reported infections or developmental abnormalities.

Six babies were conceived whilst their fathers were taking anakinra. There were no congenital or developmental abnormalities reported at follow-up of between 4 weeks and 8 years (Table 4).

DISCUSSION

Potential parents greatly wish to minimize any risks to a future child and the decision to proceed with pregnancy on novel therapies of uncertain safety remains extremely difficult for the family and their physicians. SAIDS frequently relapse rapidly after treatment withdrawal and many patients on long-term anti-IL-1 agents can only tolerate very brief suspension of treatment. Consequently simple symptomatic management throughout pregnancy is not generally feasible. In addition, uncontrolled inflammatory activity has deleterious effects on fertility and pregnancy outcomes; poorly controlled FMF is associated with a modest increase in fetal loss, preterm delivery, low birth weight and Caesarian section.(6) Male fertility is also reduced in the presence of chronic inflammation and testicular AA amyloidosis is a recognized cause of azoospermia.(7) In two fathers reported here, long term control of CAPS, first with anakinra and then canakinumab, resulted in regression of amyloid that was evident on serial SAP scintigraphy, resolution of associated nephrotic syndrome and reversal of previous infertility. Uncontrolled inflammatory disease carries its own risks to fertility, the fetus and the mother and these should be included in preconception parental counselling

The data reported here substantially increases the evidence base for anakinra and canakinumab use prior to conception, during pregnancy and breast-feeding. They include the first human data on canakinumab-exposed pregnancies and the largest reported series receiving anakinra. In general the data are reassuring for both agents and for paternal and maternal exposure. There

are no data on rilonacept and we would not advocate its use in pregnancy based on teratogenicity in animals.

There was a single case of congenital abnormality in a boy born to a mother with active refractory AOSD. AOSD is the most heterogeneous of diseases included in the study with no known genetic susceptibility and its diagnosis is based on relatively loose criteria. The patient had active disease at the time of conception, and had had considerable prior treatment including azathioprine and high-dose corticosteroids. Anakinra was initiated at nine weeks gestation. Prenatal screening identified an ectopic neurohypophysis, resulting in growth hormone deficiency, and a single kidney. Renal tract abnormalities, including unilateral renal agenesis, have been reported to occasionally occur in individuals with ectopic neurohypophysis.(8) Moreover, the latter condition has been associated with gene variants in the sonic hedgehog (SHH) pathway, (9) and SHH pathway molecules are present in the developing human renal tract.(10) Our case is important, as it is now the second report of renal agenesis in anakinra-exposed pregnancies. Chang *et al* reported a twin pregnancy in which one fetus died *in utero* and had bilateral renal agenesis.(11) The surviving twin had no developmental abnormality and was well at last reported follow-up. The mother was 19 years old in her first pregnancy having received anakinra for eight years for CAPS. She was prescribed a higher dose of anakinra at conception than in our cohort, at start of pregnancy 239 mg, increasing to 300 mg daily. She also had a history of diabetes mellitus both this and the twin pregnancy are knownrisk factors for renal tract abnormalities.(12)

Wiesel *et al* reported unilateral renal agenesis in 58 of 709,030 live births, stillbirths, and induced abortions, and 95 cases of bilateral agenesis in the same population.(13) Therefore, one case of

either renal malformation among 36 anakinra-exposed fetuses is higher than the expected frequency. Whilst experimental evidence for a direct role of the IL-1 axis in normal or abnormal renal development is currently lacking, reassuringly in an experimental murine model of a hostile uterine environment in which IL-1 is known to be elevated, inhibition of IL-1 may improve the likelihood of implantation and prevent pregnancy loss.(14), (15) Future research should seek whether IL-1 and its receptors are expressed in the normal and malformed renal tract, and the spatial and temporal relation of these molecules to those in the SHH pathway.

The current study has a number of limitations; it was retrospective and is therefore prone to errors such as recall bias and variable data collection between centers. Nonetheless this represents the best data to date and highlights the pressing need for prospective data collection, using existing registries such as EUROFEVERS (https://www.printo.it/eurofever/) or the British Society of Rheumatology Biologics Register (BSRBR) (http://www.rheumatology.org.uk/resources/bsr_biologics_registers/), and rapid feedback of relevant information to our patients and their families.

Overall the data show that the use of anakinra and canakinumab appears well tolerated, and efficacious during pregnancy and in males at conception. Serious questions remain about the increased incidence of renal tract abnormalities seen and suggests that this should be discussed with all potential parents at preconception counselling. We acknowledge that reported numbers remain small with 43 maternal cases in the literature (summarized in Table 5).

Our current practice is to advise that paternal use of IL-1 antagonists at conception appears safe, albeit based on limited clinical experience. We offer counseling for prospective parents before conception in all cases and discuss the option of temporarily ceasing IL-1 inhibiting treatment, whilst highlighting that this approach is often poorly tolerated and may carry risks to conception and fetal growth associated with uncontrolled inflammation. For women who are unable or do not wish to stop IL-1 antagonists, there are two options. First, not to conceive a child, and second, to proceed with conception and pregnancy following an informed discussion on risk-benefit. For women who do wish to become pregnant, we favor use of anakinra at the current time, based on clinical experience to date, its homology with natural IL-1Ra, and its short elimination half-life. A theoretical concern regarding canakinumab is the possibility of active transport of IgG monoclonal antibodies across the placenta from 30 weeks, and combined with the prolonged half-life of immunoglobulins in neonates, we suggest that canakinumab should not be administered from 22 weeks gestation in line with EULAR recommendations, and should be avoided where possible.

Table 1: Licensed Interleukin-1 Antagonists and evidence for their use in pregnancy and lactation

IL-1 Antagonist	Half-life	Animal data	Human Data	FDA Pregnancy Category†	Lactation
Anakinra (Kineret®, Sobi) recombinant human IL-1 receptor antagonist (IL-1 Ra)	5.7 hours (16)	No evidence of impaired fertility or fetal harm in rats or rabbits at doses > x25 human dose	5 completed pregnancies in Adult Onset Stills Disease (AOSD) (17, 18) 9 completed pregnancies in CAPS (11) See **Table 5**	B	IL-1 Ra is a normal component of breast milk. Single report; No adverse outcomes reported (18)
Canakinumab (Ilaris®, Novartis) human IgGkappa monoclonal antibody to IL-1Beta	29 Days (3)	No fetal abnormalities in Marmosets, delayed cranial ossification in mice but no teratogenicity**. (19)**	No data	C	No data
Rilonacept (ARCALYST®, Regeneron Pharmaceuticals) Dimeric, glycosylated fusion protein composed of the extracellular domains of the interleukin 1 receptor and an accessory protein IL-1-RAcP fused to the Fc domain of human IgG1	8.6 days (20)	Teratogenic in Cynomolgus monkeys**;** increased incidence of stillbirths, lumbar ribs, fusion of ribs and thoracic vertebral bodies and arches (21)	No data	C	No data

Table 1: †The United States Food and Drug Administration (FDA) Pregnancy Category B: animal studies have failed to demonstrate a risk to the fetus, there are no adequate studies in pregnant women; Category C: There are no adequate and well-controlled studies in pregnant women. Based on animal data, may cause fetal harm.

Table 2 Canakinumab Exposed Pregnancy and Breast Feeding outcomes

Maternal age at pregnancy (years)	Diagnosis	Dose and duration of canakinumab	Dates and mode of delivery	Birth weight Kgs	APGAR Score	Gender of Infant	Development	Age at last contact	Mode of feeding
25	CAPS	150mg 8 weekly PC to 8/40	38 El-CS†	3.54	10	Male	Normal	3 years	Bottle
32*	CAPS	150mg 8 weekly PC to PPT (12/40)	40 VD	4.48	10,10,10	Female	Normal	5 months	Breast
24*	CAPS	150mg 8 weekly until 36/40	40 NR	3.57	NR	Male	Normal	7 days	NR
16	CAPS	120mg single dose post conception prior to PPT	38 NR	3.29	9,9,10	Male	Normal	4 years	Breast
21	Un-SAID	300mg 8 weekly PC to D (last dose at 36/40	39 VD	NR	10,10,10	Male	Normal	1 year	NR
21	FMF	150mg 4 weekly PC-D	37 El-CS‡	3.3	“Normal”	Male	Normal	11 months	Breast
27	FMF	150mg 8 weekly PC to PPT 4/40	40 El-CS‡	3.3	“Normal”	Female	Normal	3.5 years	Breast
26†	Cogan Syndrome	150mg 4 weekly PC-6/40	Miscarriage 6/40						

Table 2: Kgs Kilograms, Un-SAID uncharacterized systemic autoinflammatory disease, PC prior to conception, PPT confirmation of pregnancy (positive pregnancy test) , D delivery, VD vaginal delivery, I-VD induced vaginal delivery, EM-CS emergency cesarean section, EL-CS elective cesarean section, NR not reported, CAPS Cryopyrin Associated Periodic Fever Syndromes, FMF Familial Mediterranean fever, AOSD Adult Onset Stills Disease, TRAPS TNR Receptor Associated Periodic Fever Syndrome,† due to gestational diabetes ‡ due to patient choice, * denotes patient who received both canakinumab and anakinra during same pregnancy, †denotes same patient who received both canakinumab and anakinra in two separate pregnancies both resulting in miscarriage (see also Table 3).

Table 3 Anakinra Exposed Pregnancy and Breast Feeding Outcomes

Maternal age at pregnancy (years)	Diagnosis	Dose and duration of anakinra	Dates (weeks) & Mode of delivery	Birth weight (kg)	APGAR	Gender	Development	Age at last contact	Mode of Feeding
29	CAPS	50mg alt/days PC to D	39 I-VD	3.94	9,9,9	Male	Normal	4 years	Bottle
32	CAPS	50mg alt/days PC to D	39 VD	NR	NR	Female	Normal	2 years	Bottle
30	CAPS	100mg daily PC to D	41+1 VD	3.6	9,9,10	Male	Normal	2 years	Breast
32*	CAPS	100mg daily PPT to D	40 VD	4.48	10	Female	Normal	5 Months	Breast
24*	CAPS	100mg daily 36/40 to D	40 NR	3.57	NR	Male	Normal	7 days	NR
20	CAPS	100mg PC to PPT	36+6 NR	2.83	10,10,10	Male	Normal	10 weeks	Bottle
24	CAPS	100mg PC to D	38+6 EM-CS[1]	NR	NR	NR	Normal	6 months	NR
34	CAPS	100mg daily PC to 6/40	40 El-CS[2]	NR	NR	Male	Normal	18 months	NR
25	CAPS	100mg daily PC to D	NR	NR	NR	Male	Normal	8 years	Breast 10/12
35	CAPS	100mg daily Dates NR	40+1 NR	NR	NR	Female	Normal	NR	NR
38	CAPS	100mg Dates NR	NR	NR	NR	Female	Normal	NR	NR
28	CAPS	100mg Dates NR	NR	NR	NR	Female	Normal	NR	NR
33	FMF	100mg daily	36+1	2.17	8	Male	Normal	2 years	Breast

		PC-D	El-CS[3]						
28	FMF	100mg daily 12/40 to D	40 VD	3.17	10	Female	Normal	19 months	Breast 3/12
24	FMF	100mg daily PC-D	36 VD	1.6	7	Female	Normal	9 months	Breast
38	Idiopathic Pericarditis	100mg daily PC to PPT	38+2 VD	2.93	8,9,9	Male	Normal	12 weeks	Bottle
29	AOSD	200-300mg daily PC-16/40	37	2.45	9	Female	Normal	10 months	Bottle
31	AOSD	100mg daily 22/40-32/40 Then alt days to 33/40	35+1 NR	2.02	9	Male	Normal	18 months	Breast
30	AOSD	100 mg daily 9/40 to D	38+1 El-CS[2]	NR	7,8,9	Male	- Left Renal Agenesis - Ectopic Neurohypophysis with growth hormone deficiency	1 year 3months	Breast 3/12
29	AOSD	100mg daily NR	38 VD	3.06	Normal	Female	Normal	9 months	Breast
29	TRAPS	100mg daily PC to D	41 I-VD	3.23	9,9,9	Male	Normal	8 months	Breast
29	TRAPS	100mg PC to D	NR	NR	NR	Female	Normal	NR	NR
25†	Cogan Syndrome	200mg daily PC-12/40	Miscarriage 12/40						

Table 3: PC prior to conception, PPT confirmation of pregnancy (positive pregnancy test) , D delivery, VD vaginal delivery, I-VD induced vaginal delivery, EM-CS emergency cesarean section, EL-CS elective cesarean section, NR not reported, CAPS Cryopyrin Associated Periodic Fever Syndromes, FMF Familial Mediterranean fever, AOSD Adult Onset Stills Disease, TRAPS TNR Receptor Associated Periodic Fever Syndrome, mg miligrams, kg kilograms, [1]failure to progress, [2]patient choice, [3]per vaginal bleed started at 34/40, * denotes patient who received both canakinumab and anakinra during same pregnancy, †denotes same patient who received both canakinumab and anakinra in two separate pregnancies both resulting in miscarriage (see also Table 2).

Table 4 Pregnancies with Paternal Exposure to Anakinra or Canakinumab at conception:

Diagnosis	Number of offspring exposed	Drug/Dose	Drug duration prior to conception (months)	Congenital Abnormalities	Developmental Abnormalities	Gender	Age at last contact
AOSD	1	Anakinra 100mg daily	Not known	None	None	Female	4 weeks
AOSD	1	Anakinra 100mg daily	Not Known	None	None	Female	10 months
CAPS	3	Canakinumab 150mg 8 weekly	248	None	None	Male	10 years
			75	None	None	Male	8 years
				None	None	Female	4 years
CAPS	1	Anakinra 100mg daily	25	None	None	Male	8 years
CAPS	1	Canakinumab 150mg 8 weekly	23	None	None	Male	7 years
TRAPS	2	Anakinra 100mg alternate days	3	None	None	Male	5 years
			57	None	None	Female	6 months
TRAPS	1	Anakinra 100mg daily	66	None	None	Male	16 months
TRAPS	1 (IVF)	Canakinumab 150mg 8 weekly	24	None	None	Female	2 years

Table 4 Legend:

AOSD Adult Onset Stills Disease, CAPS Cryopyrin Associated Periodic Fever Syndromes, TRAPS Tumour Necrosis Factor Receptor Associated Periodic Fever Syndrome, IVF In Vitro Fertilization.

Table 5: Summary of previously published data on anakinra use in pregnancy

Reference	Maternal Diagnosis	Treatment and dose	Delivery	Birth weight (kgs)	APGAR Score	Gender	Development	Duration of follow up	Method of feeding
Berger 2009 (18)	AOSD	Anakinra 100mg daily 2 years prior to and through pregnancy and delivery	VD	2.7 kg	7,8,9	Female	Normal	4 months	Breast
Fischer Betz (22) Case 1	AOSD	Anakinra 100mg daily, 1 year prior to pregnancy and throughout	VD 39/40	3.1 kg	NR	Male	Normal	NR	Bottle
Fischer Betz Case 2	AOSD	Anakinra 100mg daily 12/40 onwards	CS 36/40	2.8 kg	NR	Male	Normal	NR	Bottle
Chang 2014(11) Case 1	CAPS	Anakinra	VD 41/40	3.74 kg	NR	NR	NR	NR	Bottle
Chang 2014 Case 2	CAPS	Anakinra	VD 41/40	3.63 kg	NR	NR	NR	NR	Bottle
Chang 2014 Case 3	CAPS	Anakinra	VD 38/40	3.40 kg	NR	NR	NR	NR	Breast 3 months
Chang 2014 Case 4	CAPS	Anakinra	VD 37/40	3.46 kg	NR	NR	NR	NR	Bottle

Chang 2014	CAPS	Anakina	VD	2.98 kg	NR	NR	NR	NR	Bottle
Case 5			37.5/40						
Chang 2014	CAPS	Anakinra	VD	3.35 kg	NR	NR	NR	NR	Bottle
Case 6			39/40						
Chang 2014	CAPS	Anakinra	CS	4.14 kg	NR	NR	NR	NR	Breast
Case 7			40/40						1Year
Chang 2014	CAPS	Anakinra	VD	2.64 kg	NR	NR	NR	NR	Breast
Case 8*			38.7/40						< 1 month
Chang 2014	CAPS	Anakinra	CS	3.52 kg	NR	NR	NR	NR	Bottle
Case 9			“term”						

Table 5: CAPS Cryopyrin Associated Periodic Syndrome, VD Vaginal Delivery, CS Cesarean Section, NR not recorded * twin dichorionic-diamniotic pregnancy with fetal demise of one fetus with bilateral renal agenesis, surviving twin had no congenital abnormality.

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