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Concise report

International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors

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Abstract

Objective. To provide 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 centre. A uniform data collection sheet was used to obtain standardized data including maternal age and diagnosis, type, duration of and response to IL-1 blockade, 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 five to canakinumab, with no negative outcomes. We also report the first data on canakinumab-exposed pregnancies: eight pregnancies that resulted in the delivery of seven 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.

Key words: interleukin-1 inhibitors, anakinra, canakinumab, pregnancy, autoinflammatory disease, CAPS, TRAPS, biologic therapies, familial Mediterranean fever, adult onset stills disease

CLINICAL SCIENCE

Rheumatology key messages

- Anakinra and canakinumab are well tolerated in pregnancy but data on safety remain limited.
- Anakinra is the preferred agent in pregnancy due to larger evidence base and short half-life.
- Limited data on anakinra and canukinumab suggest it is safe in males prior to conception.

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Introduction

The first IL-1 inhibitor was licensed for use in RA in 2001, but 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 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, 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 with 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], and while 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 offspring born to fathers receiving IL-1 antagonists. Currently there are three IL-1 antagonists, anakinra, canakinumab and rilonacept (supplementary Table S1, available at *Rheumatology* Online).

To create a much needed evidence base to inform decision making for our patients, the international autoinflammatory disease community has shared data to provide an evidence base and suggested recommendations for managing conception and pregnancy in this group of patients.

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 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 eight were maternal and 29 anakinra-exposed pregnancies of which 23 were maternal (Table 1). We report the first data on paternal exposure to anakinra (n = 6) and canakinumab (n = 5) (Table 2). We report the outcome of 14 neonates breast fed by mothers taking anakinra (n = 10) or canakinumab (n = 4) for up to 10 months duration, with no reported serious infections (Table 1). 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 favourable safety and efficacy profiles of these medications, there were no reported serious infections in the mothers or 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 1). A single case of miscarriage occurred at 6 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 150 mg 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), and all were in complete clinical and biochemical remission for cryopyrin-associated periodic fever syndromes (CAPS) (n = 4), familial mediterranean fever (FMF) (n = 2) and one case of unexplained inflammatory illness. Pregnancies were uneventful, all reaching full term and normal birth weight; mean 3.58 kg (range 3.3–4.48 kg). Data on mode of delivery were available for five cases, with three caesarean 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 first trimester, at 8 and 12 weeks, respectively. Two mothers switched to anakinra, at 8 and 36 weeks, and one was treated from before conception to term with 300 mg 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 TNR receptor-associated periodic fever syndrome (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. Sixty-six per cent of the offspring were male (Table 2). At mean follow-up of 6.83

Table 1 IL-1-exposed pregnancy and breast feeding outcomes; maternal exposure

IL-1 inhibitor	Maternal age at pregnancy (years)	Diagnosis	Dose and duration of anakinra	Dates (weeks) and mode of delivery	Birth weight (kg)	APGAR	Gender	Development	Age at last contact	Mode of feeding
Canakinumab	25	CAPS	150 mg 8 weekly PC to 8/40	38 EI-CS[a]	3.54	10	Male	Normal	3 years	Bottle
Canakinumab	32[b]	CAPS	150 mg 8 weekly PC to PPT (12/40)	40 VD	4.48	10, 10, 10	Female	Normal	5 months	Breast
Canakinumab	24[b]	CAPS	150 mg 8 weekly until 36/40	40 NR	3.57	NR	Male	Normal	7 days	NR
Canakinumab	16	CAPS	120 mg single dose post-conception prior to PPT	38 NR	3.29	9, 9, 10	Male	Normal	4 years	Breast
Canakinumab	21	Un-SAID	300 mg 8 weekly PC to D, last dose at 36/40	39 VD	NR	10, 10, 10	Male	Normal	1 year	NR
Canakinumab	21	FMF	150 mg 4 weekly PC to D	37 EI-CS[c]	3.3	'Normal'	Male	Normal	11 months	Breast
Canakinumab	27	FMF	150 mg 8 weekly PC to PPT 4/40	40 EI-CS[c]	3.3	'Normal'	Female	Normal	3.5 years	Breast
Canakinumab	26[d]	Cogan Syndrome	150 mg 4 weekly PC to 6/40	Miscarriage 6/40						
Anakinra	29	CAPS	50 mg alt days PC to D	39 I-VD	3.94	9, 9, 9	Male	Normal	4 years	Bottle
Anakinra	32	CAPS	50 mg alt days PC to D	39 VD	NR	NR	Female	Normal	2 years	Bottle
Anakinra	30	CAPS	100 mg daily PC to D	41 + 1 VD	3.6	9, 9, 10	Male	Normal	2 years	Breast
Anakinra	32[b]	CAPS	100 mg daily PPT to D	40 VD	4.48	10	Female	Normal	5 Months	Breast
Anakinra	24[b]	CAPS	100 mg daily 36/40 to D	40 NR	3.57	NR	Male	Normal	7 days	NR
Anakinra	20	CAPS	100 mg PC to PPT	36 + 6 NR	2.83	10, 10, 10	Male	Normal	10 weeks	Bottle
Anakinra	24	CAPS	100 mg PC to D	38 + 6 EM-CS[e]	NR	NR	NR	Normal	6 months	NR
Anakinra	34	CAPS	100 mg daily PC to 6/40	40 EI-CS[c]	NR	NR	Male	Normal	18 months	NR
Anakinra	25	CAPS	100 mg daily PC to D	NR	NR	NR	Male	Normal	8 years	Breast 10/12
Anakinra	35	CAPS	100 mg daily, dates NR	40 + 1 NR	NR	NR	Female	Normal	NR	NR

(continued)

Table 1 Continued

IL-1 inhibitor	Maternal age at pregnancy (years)	Diagnosis	Dose and duration of anakinra	Dates (weeks) and mode of delivery	Birth weight (kg)	APGAR	Gender	Development	Age at last contact	Mode of feeding
Anakinra	38	CAPS	100 mg, dates NR	NR	NR	NR	Female	Normal	NR	NR
Anakinra	28	CAPS	100 mg, dates NR	NR	NR	NR	Female	Normal	NR	NR
Anakinra	33	FMF	100 mg daily PC to D	36 + 1 El-CS[f]	2.17	8	Male	Normal	2 years	Breast
Anakinra	28	FMF	100 mg daily 12/40 to D	40 VD	3.17	10	Female	Normal	19 months	Breast 3/12
Anakinra	24	FMF	100 mg daily PC to D	36 VD	1.6	7	Female	Normal	9 months	Breast
Anakinra	38	Idiopathic Pericarditis	100 mg daily PC to PPT	38 + 2 VD	2.93	8, 9, 9	Male	Normal	12 weeks	Bottle
Anakinra	29	AOSD	200–300 mg daily PC to 16/40	37	2.45	9	Female	Normal	10 months	Bottle
Anakinra	31	AOSD	100 mg daily 22/40–32/40, then alt days to 33/40	35 + 1 NR	2.02	9	Male	Normal	18 months	Breast
Anakinra	30	AOSD	100 mg daily 9/40 to D	38 + 1 El-CS[c]	NR	7, 8, 9	Male	Left renal agenesisEctopic neurohypophysis with growth hormone deficiency	1 year 3 months	Breast 3/12
Anakinra	29	AOSD	100 mg daily NR	38 VD	3.06	Normal	Female	Normal	9 months	Breast
Anakinra	29	TRAPS	100 mg daily PC to D	41 I-VD	3.23	9, 9, 9	Male	Normal	8 months	Breast
Anakinra	29	TRAPS	100 mg PC to D	NR	NR	NR	Female	Normal	NR	NR
Anakinra	25[d]	Cogan Syndrome	200 mg daily PC to 12/40	Miscarriage 12/40						

[a]Due to gestational diabetes. [b]Patient who received both canakinumab and anakinra during same pregnancy. [c]Due to patient choice. [d]Patient who received both canakinumab and anakinra in two separate pregnancies both resulting in miscarriage. [e]Failure to progress. [f]Per vaginal bleed started at 34/40. AOSD: adult onset stills disease; CAPS: cryopyrin-associated periodic fever syndromes; D: delivery; EL-CS: elective caesarean section; EM-CS: emergency cesarean section; FMF: familial mediterranean fever; I-VD: induced vaginal delivery; NR: not reported; PC: prior to conception; PPT: confirmation of pregnancy (positive pregnancy test); TRAPS: TNR receptor-associated periodic fever syndrome; Un-SAID: uncharacterized systemic autoinflammatory disease; VD: vaginal delivery.

Table 2 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 100 mg daily	Not known	None	None	Female	4 weeks
AOSD	1	Anakinra 100 mg daily	Not known	None	None	Female	10 months
CAPS	3	Canakinumab 150 mg 8 weekly	248	None	None	Male	10 years
			75	None	None	Male	8 years
				None	None	Female	4 years
CAPS	1	Anakinra 100 mg daily	25	None	None	Male	8 years
CAPS	1	Canakinumab 150 mg 8 weekly	23	None	None	Male	7 years
TRAPS	2	Anakinra 100 mg alternate days	3	None	None	Male	5 years
			57	None	None	Female	6 months
TRAPS	1	Anakinra 100 mg daily	66	None	None	Male	16 months
TRAPS	1 (IVF)	Canakinumab 150 mg 8 weekly	24	None	None	Female	2 years

AOSD: adult onset stills disease; CAPS: cryopyrin-associated periodic fever syndromes; IVF: *in vitro* fertilization; TRAPS: TNF receptor-associated periodic fever syndrome.

(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

Twenty-nine pregnancies were exposed to anakinra in total, 23 through maternal exposure, resulting in the births of 28 infants (Table 1). 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 the exception of the two women with AOSD and Cogan syndrome, whose diseases were less well suppressed. Thirty-nine per cent 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 200 mg 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 100 mg before conception and continued it until 25/40.

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

All babies were born healthy with normal Appearance, Pulse, Grimace, Activity and Respiration scores at 10 min 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 9 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 10 months with no reported infections or developmental abnormalities. Six babies were conceived while their fathers were taking anakinra. There were no congenital or developmental abnormalities reported at follow-up of between 4 weeks and 8 years (Table 2).

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 caesarean 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 increase the evidence base for anakinra and canakinumab use prior to conception and during pregnancy and breast-feeding (supplementary Table S2, available at *Rheumatology* Online). 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 AZA and high-dose corticosteroids. Anakinra was initiated at 9 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.* [11] reported a twin pregnancy in which one fetus died *in utero* and had bilateral renal agenesis. 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 8 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 and both this and the twin pregnancy are known risk factors for renal tract abnormalities [12].

Wiesel *et al.* [13] 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. Therefore, one case of either renal malformation among 36 anakinra-exposed fetuses is higher than the expected frequency. While 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 centres. 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 (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 this suggests that this should be discussed with all potential parents at preconception counselling. We acknowledge that reported numbers remain small with only 12 previously reported maternal cases of anakinra exposure in the literature (summarized in supplementary Table S2, available at *Rheumatology* Online).

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 counselling for prospective parents before conception in all cases and discuss the option of temporarily ceasing IL-1 inhibiting treatment, while 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 favour 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.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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