Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra)

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ABSTRACT

Adult onset Still's disease (AOSD) is an uncommon, systemic, inflammatory disorder of unknown etiology, characterised by spiking fevers, skin rash, and arthritis. Treatment consists of glucocorticosteroids and immunosuppressive drugs. Over the last few years it has become increasingly evident that treatment with the IL-1 receptor antagonist (IL-1RA) anakinra is highly effective even in patients with intractable disease. So far, there are scant data available on the effects of anakinra in pregnancy. We report two patients with AOSD who successfully gave birth while treated with anakinra during pregnancy.

Introduction

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterised by a variety of clinical features, including intermittent spiking fever, an evanescent salmon pink rash, arthritis and multi-organ involvement (1). AOSD falls into the category of auto-inflammatory diseases, which are uniquely mediated by IL–1β. Blockade of IL-1 signalling often has a dramatic and sustained effect in AOSD patients with cessation of symptoms and significant decrease of acute phase markers (2-4). IL-1 receptor antagonist anakinra therefore is increasingly used after corticosteroids and immunosuppressive drugs have failed or have induced serious adverse effects. Anakinra has been assigned to pregnancy category B by the FDA, indicating that animal studies have failed to reveal evidence of foetal harm but there is insufficient evidence in humans. Treatment with anakinra therefore is not recommended during pregnancy. However, in individual cases, benefit of treatment has to be judged against risks associated with active inflammatory disease during pregnancy. We describe two cases of use of anakinra in women with AOSD during pregnancy.

Case reports

Case 1

A 27-year-old woman presented in 2005 with a history of intermittent AOSD since 2002 (fever, pharyngitis, arthralgia, pericarditis, pleuritis, leucocytosis, hyperferritinaemia [22.000 ng/ml, normal range 40-200 ng/ml]). Her disease course was refractory to treatment with prednisone alone or in combination with methotrexate, azathioprine, cyclosporine or etanercept. In 2007 during a severe flare with pericarditis and pleural effusion, anakinra was initiated at 100 mg/day. The patient became rapidly asymptomatic and prednisone was tapered to 5 mg/day. In 2008, during a 5 day interval without anakinra injections because of lack of medication, she again developed fever and pleuritic pain. After reuptake of anakinra treatment she remained in remission. In May 2009 she presented herself in the 8th week of unplanned pregnancy. She was informed about the lack of knowledge of the effects of anakinra on foetal development but decided to continue anakinra during pregnancy. The adjusted risk for trisomy-21 based on age, β-HCG, PAPP-A and length of the nuchal fold was 1:356. Alpha-fetoprotein was normal. Ultrasound repeatedly demonstrated normal growth, no evidence of malformation and Doppler analysis of the uterine artery was always normal. The patient showed only transient arthralgia during pregnancy and remained free of other signs of AOSD. She gave spontaneous birth to a healthy boy at 39 weeks of gestation (weight 3100 gr, length 50 cm; APGAR score 9/9/10). There were no pathological findings on paediatric examination at discharge. The mother decided not to breastfeed under continuation of treatment with anakinra. She has so far remained free of signs of AOSD.

Case 2

A 29-year-old woman (gravida 2, para 1) presented in 2010 during her 12th week of pregnancy with high fever, polyarthritis, hepatosplenomegaly, nonpruric rash, pharyngitis, leucocytosis, elevated C-reactive protein 11.1 (<0.3) mg/dl and hyperferritinaemia (>40.000 ng/ml). She had an extensive evaluation that led to the diagnosis of AOSD. Treatment with prednisone up to 100 mg/day was only of partial effect. During follow-up, prednisone dosage could not be reduced below 60 mg/d because of severe arthralgia, myalgia, pharyngi-

tis, fever up to 39° and unchanged acute phase markers. The limited therapeutic possibilities as well as the high risk for complications associated with continuous use of high dosages of glucocorticoids during pregnancy (like diabetes, hypertension, preeclampsia, prematurity) were intensively discussed with the patient. Especially the use of cyclosporine A and azathioprine was considered but rejected because of concern that a steroid sparing effect would have been seen only after several weeks**.** After careful consideration, treatment with anakinra was subsequently started, which led to prompt remission of all symptoms and normalisation of C-reactive protein. The prednisone dosage was reduced to 5 mg/day. She delivered a healthy boy (weight 2800 gr, length 47 cm, APGAR Score 8/9/9) at 36 weeks of gestation by Cesaerean section. The mother also did not breastfeed under continuation of treatment with anakinra. During the next months, anakinra was tapered and finally stopped. Shortly after, the patient developed a flare and she too has, so far, been successfully treated with anakinra.

Discussion

We report two patients with AOSD who successfully gave birth while treated with anakinra during pregnancy. Until now, there has been only one published case report of successful continuous treatment of AOSD during pregnancy and breastfeeding (5).

The relation between female hormones, cytokines, and disease activity during and after pregnancy has not been reported in AOSD. Small series of pregnancies in women with AOSD showed an increased risk for adverse outcomes of pregnancy like preterm birth and intrauterine growth retardation and it has been discussed that disease activity is of possible influence on pregnancy outcome (6). It is well known that women with chronic inflammatory arthritides, most specifically rheumatoid arthritis (RA), have an increased risk of prematurity, small for gestation babies and preeclampsia (7). Disease relapse in patients with known AOSD occurred most commonly in the post-partum period, when reactivations of other inflammatory rheumatic diseases like RA are also often observed. Studies that have detailed data available throughout RA pregnancies suggest an inverse relationship between disease activity and pregnancy outcome (8). This suggests that improved control of inflammation during pregnancy may lead to better pregnancy outcomes.

The cytokine network plays an important role in a wide range of reproductive and pregnancy related processes. The placenta and extraplacental membranes (gestational tissues) are sources of a large number of cytokines throughout normal gestation. Plasma concentrations of several cytokines have been shown to change with the stage of pregnancy. Although some physiological roles of proinflammatory cytokines at the maternal-foetal interface have been described with regard to growth of the placenta and decidua, much of the literature supports the concept that excessive or aberrant production of proinflammatory cytokines such as IL-1, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ at the maternal-foetal interface is harmful to pregnancy (9).

Both trophoblasts and placental macrophages produce IL-1 over the course of gestation (10). IL-1 can act on a number of cell types to increase the production of cyclooxygenase (COX)-2 and prostaglandin E_2 (PGE_2). PGE_2 is the most effective molecule for inducing cervical dilation in women and has also been related to an increased risk of preterm birth in animal models (11, 12, 13). In addition, regulatory molecules like tumour necrosis factor receptors (TNFR) or IL-1RA have been found increased during pregnancy. IL-1RA is a naturally occurring IL-1R blocker that inhibits the proinflammatory effects of IL-1. It is physiologically present in the foetal, maternal, and amniotic fluid compartments. Studies of human placentas showed that amnion, chorion, and predominantly decidua can release or secrete IL-1RA (14). IL-1RA likely has pleiotropic effects in pregnancy. On the one hand, IL-1RA has the potential to inhibit embryonic implantation in mice (15). On the other hand, outcomes more favourable in an animal model with experimentally induced sepsis and hypoxia and treatment with IL-1RA have been described (16). In this latter setting, an imbalance between pro- and anti-inflammatory responses has been implicated in the pathogenesis of infection-related preterm labour. In accordance with this, IL-1β, but not IL-1RA, levels are elevated in the amniotic fluid of pregnancies complicated by intra-amniotic infection (17). Physiologically, circulating maternal IL-1RA levels increase with advancing gestational age in pregnancy, and this has also been noted in women with RA (18). Interestingly, an increase of IL-1RA from the second to the third trimester has been shown to correspond with low disease activity in RA pregnancies (18). Thus, higher levels of IL-1RA might lead to improvement of diseases mediated by IL–1.

Anakinra is a recombinant form of the human IL-1RA. It consists of 153 amino acids and has a molecular weight of 17 KD. Anakinra has been shown to cross the placenta (19) and thereby could influence the capability of placental tissues to produce IL1-RA. Toxicology studies in animals have not indicated direct or indirect harmful effects of anakinra with respect to fertility, pregnancy, embryonal/foetal development, parturition, or peri- and postnatal development at doses up to 100 times the human dose (20). Recently, maternal anakinra therapy was used successfully during pregnancy in rats to protect various tissues against inflammatory aggressions (16). However, there are no adequate data from the use of anakinra in pregnant women, therefore, use during pregnancy is not recommended unless clearly indicated.

In our two patients, ankinra was very effective in suppressing disease activity of AOSD and apparently did not affect the development of the child in utero or post partum. It is difficult to confirm the safety of any medication during pregnancy. Owing to very limited experience from treatment throughout pregnancy and an absence of knowledge about the possible long-term effects on exposed children, however, the potential risks of inhibiting IL1 prior to conception and throughout pregnancy must be carefully discussed with the patients.

References

1. KONTZIAS A, EFTHIMIOU P: Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs* 2008; 68: 319-17.
2. FITZGERALD AA, LECLERCQ SA, YAN A, HOMIK JE, DINARELLO CA: Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum* 2005; 52: 1794-93.
3. LEQUERRE T, QUARTIER P, ROSELLINI D *et al*.: Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 2008; 67: 302-8.
4. WOO P: Anakinra treatment for systemic juvenile idiopathic arthritis and adult onset Still disease. *Ann Rheum Dis* 2008; 67: 281-2.
5. BERGER CT, RECHER M, STEINER U, HAUSER TM: A patient's wish: anakinra in pregnancy. *Ann Rheum Dis* 2009; 68: 1794-5.
6. MOK MY, LO Y, LEUNG PY, LAU CS: Pregnancy outcome in patients with adult onset Still's disease. *J Rheumatol* 2004; 31: 2307-9.
7. CHAKRAVARTY EF, NELSON L, KRISHNAN E: Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 899-907.
8. DE MAN YA, HAZES JM, VAN DER HEIDE H *et al*.: Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009; 60: 3196-206.
9. CROY BA, CHANTAKRU S, ESADEG S, ASHKAR AA, WEI Q: Decidual natural killer cells: key regulators of placental development (a review) *J Reprod Immunol* 2002; 57: 151-68.
10. MARVIN KW, KEELAN JA, EYKHOLT RL, SATO TA, MITCHELL MD: Use of cDNA arrays to generate differential expression profiles for inflammatory genes in human gestational membranes delivered at term and preterm. *Mol Hum Reprod* 2002; 8: 399-408.
11. BAGGIA S, GRAVETT MG, WITKIN SS, HALUSKA GJ, NOVY MJ: Interleukin-1 beta intra-amniotic infusion induces tumor necrosis factor-alpha, prostaglandin production, and preterm contractions in pregnant rhesus monkeys. *J Soc Gynecol Investig* 1996; 3: 121-6.
12. SADOWSKY DW, ADAMS KM, GRAVETT MG *et al*.: Preterm labor is induced by intraamniotic infusions of interleukin-1beta and tumor necrosis factor-alpha but not by interleukin-6 or interleukin-8 in a nonhuman primate model. *Am J Obstet Gynecol* 2006; 195: 1578-9.
13. MURTHA AP, NIEVES A, HAUSER ER *et al*.: Association of maternal IL-1 receptor antagonist intron 2 gene polymorphism and preterm birth. *Am J Obstet Gynecol* 2006; 195: 1249-53.
14. FIDEL PL JR, ROMERO R, RAMIREZ M *et al*.: Interleukin-1 receptor antagonist (IL-1RA) production by human amnion, chorion, and decidua. *Am J Reprod Immunol* 1994; 32: 1-7.
15. SIMÓN C, FRANCES A, PIQUETTE GN *et al*.: Embryonic implantation in mice is blocked by interleukin-1 receptor antagonist. *Endocrinology* 1994; 134: 521-8.
16. GIRARD S, TREMBLAY L, LEPAGE M, SÉBIRE G: IL-1 receptor antagonist protects against placental and neurodevelopmental defects induced by maternal inflammation. *J Immunol* 2010; 184: 3997-4005.
17. ROMERO R, GOMEZ R, GALASSO M *et al*.: The natural interleukin-1 receptor antagonist in the fetal, maternal, and amniotic fluid compartments: the effect of gestational age, fetal gender, and intrauterine infection. *Am J Obstet Gynecol* 1994; 171: 912-21.
18. ØSTENSEN M, FÖRGER F, NELSON JL, SCHUHMACHER A, HEBISCH G, VILLIGER PM: Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis* 2005; 64: 839-44.
19. McDuffie RS Jr, Davies JK, Leslie KK, Lee S, Sherman MP, Gibbs RS: A randomized controlled trial of interleukin-1 receptor antagonist in a rabbit model of ascending infection in pregnancy. *Infect Dis Obstet Gynecol* 2001; 9: 233-7.
20. Kineret® (anakinra) [summary of product characteristics]. Europe B.V.; 2003. http://www.kineret-eu.com/en/pro/faq/arifaq36.jsp.