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Cardiovascular imaging

Anakinra during pregnancy and lactation for corticosteroid-dependant colchicine-resistant recurrent pericarditis in a patient with neutralizing anti-interleukin-1 receptor antagonist antibodies: a case report

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Background Anakinra, an interleukin-1 receptor antagonist (IL-1 Ra), is a treatment option for recurrent pericarditis refractory to conventional therapy. However, some patients cannot discontinue anakinra treatment without relapse. This is of particular concern for women of childbearing age, as data on its safety during pregnancy and lactation is limited.

Case summary We report the case of a 36-year-old White woman with recurrent pericarditis of an inflammatory phenotype. Pericardial biopsy revealed virus-negative fibro-productive pericarditis, and genetic testing showed no identifiable cause. Despite treatment with non-steroidal anti-inflammatory drugs, colchicine, and corticosteroids, the patient experienced multiple recurrences and developed corticosteroid-related side effects. Introduction of anakinra resulted in immediate clinical improvement and allowed corticosteroid withdrawal. However, several attempts to discontinue anakinra led to pericarditis recurrences. The patient tested positive for neutralizing anti-IL-1Ra antibodies. During the stable phase of the disease, as confirmed by cardiac magnetic resonance imaging, and while on anakinra and colchicine, she conceived spontaneously. She maintained anakinra treatment throughout the full-term pregnancy and breastfeeding, with no impact on foetal or child development.

Discussion Our paper provides evidence supporting the safe use of anakinra in pregnancy and lactation in a patient with recurrent pericarditis. It also reports the first case of anti-IL-1Ra antibodies in a patient receiving anakinra for recurrent pericarditis, which may help explain the dependency on the medication. The potential role of these antibodies as biomarkers for anakinra dependency or tools for optimizing immunosuppressive treatment warrants further research. A patient-centred counselling and a multidisciplinary approach are essential for achieving optimal outcomes.

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ESC curriculum 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 6.6 Pericardial disease • 9.8 Pregnancy with cardiac symptoms or disease

Learning points

- Managing recurrent pericarditis during pregnancy requires a personalized approach weighing the risks of sub-optimal treatment with potential effects of drug exposure on foetal development.
- Anakinra, an IL-1 antagonist, is effective for recurrent pericarditis resistant to conventional therapy and may be continued during pregnancy and lactation when no other treatment options are available.
- The presence of neutralizing anti-IL-1Ra antibodies may explain anakinra dependency but their exact pathophysiological role in recurrent pericarditis warrant further research.

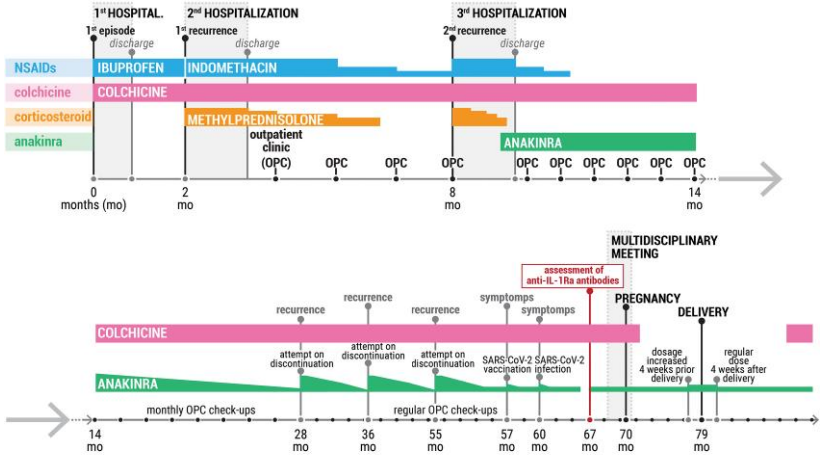
Introduction

Recurrent pericarditis occurs in 15%–30% of patients with acute pericarditis and is associated with significant morbidity due to repeating symptoms and medication-related side effects.[1] It is presumed to be caused by viral infections or immune-related processes, involving either an autoinflammatory mechanism of the innate immune system or an autoimmune response of the adaptive immune system.[2] Autoinflammatory mechanism is characterized by excessive production of interleukin-1(IL-1)β due to dysregulated activation of the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome. Genetic variants influencing innate immune response may play an important role.[3] The result is recurrent pericarditis with an inflammatory phenotype presenting with intermittent inflammatory attacks with fever, serositis, and elevated C-reactive protein (CRP) levels. The described autoinflammatory mechanism is regulated by an anti-inflammatory cytokine IL-1 receptor antagonist (IL-1Ra), which inhibits the binding of IL-1 to its receptor.

Often first and second line therapy, including non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids, is not successful. Anakinra, a recombinant human IL-1Ra that binds to the IL-1 receptor (IL-1R), inhibiting both IL-1α and β pro-inflammatory activity, emerged as a novel treatment option in corticosteroid-dependent, colchicine-resistant recurrent pericarditis.[4] However, a certain proportion of patients is unable to discontinue anakinra treatment without relapse of the disease. This phenomenon is of particular concern in female patients of childbearing age since safety data on anakinra treatment during pregnancy and lactation is limited. The presence of neutralizing anti-IL-1Ra antibodies might be involved, however their role in the pathogenesis of the disease and in the response to treatment remains to be elucidated.[5,6]

We report the case of a young woman with corticosteroid-dependent, colchicine-resistant recurrent pericarditis, who tested positive for anti-IL-1Ra antibodies. She responded well to anakinra but was unable to discontinue treatment without experiencing a relapse. Consequently, she continued anakinra therapy throughout both pregnancy and lactation. To the best of our knowledge, this is the first reported case of the presence of anti-IL-1Ra antibodies in a patient with recurrent pericarditis undergoing long-term anakinra treatment.

Summary figure



All pericarditis episodes were characterized by typical chest pain and elevated CRP.

Timeline of events depicting pericarditis episodes and treatment regimen.

Case presentation

We present the case of a 36-year-old White woman with recurrent pericarditis (*Summary figure*). At first pericarditis manifestation she was 29 years-old and already had a complex medical history with a spectrum of immune-mediated conditions, including celiac disease, secondary hypothalamic-pituitary–adrenal axis insufficiency treated with hydrocortisone, hypothyroidism following autoimmune thyroiditis and radioiodine treatment, Raynaud's phenomenon, human leucocyte antigen (HLA) B27 positivity, and high anti-nuclear antibody (ANA) titres (≥ 1:160). She presented with severe pericarditic chest pain and fever. Her heart rate was 126 beats per minute and blood pressure 90/70 mmHg. Physical examination revealed muffled heart sounds, but no appreciable pericardial rub. No peripheral oedema or pulmonary crackles were present. Laboratory results showed elevated inflammatory markers, with a CRP level of 108 mg/L and a leucocyte count of 15 $\times 10^9$/L, while troponin I remained within the normal range. Electrocardiogram (ECG) revealed sinus tachycardia, low QRS voltages, and subtle diffuse ST elevation with PR depression. Chest X-ray demonstrated a small pleural effusion, while echocardiography confirmed a moderate pericardial effusion with evidence of hemodynamic compromise. Urgent pericardiocentesis was performed and 190 mL of serous fluid was withdrawn. A comprehensive diagnostic workup excluded microbiological, rheumatoid, malignant and metabolic causes of pericarditis. She received initial treatment with ibuprofen 600 mg three times daily and colchicine 0.5 mg once daily.

Two months later, after slow tapering of ibuprofen, she suffered the first recurrence with fever and increased CRP level of 125 mg/L. Cardiac magnetic resonance imaging (MRI) showed a small pericardial effusion and a thickened pericardium of 4 mm, along with signs of active inflammation, including late gadolinium enhancement (LGE) and increased signal intensity on short tau inversion recovery (STIR-T2w) sequences (*Figure 1*). There were no signs of constrictive physiology or myocardial involvement. A pericardial biopsy was performed and

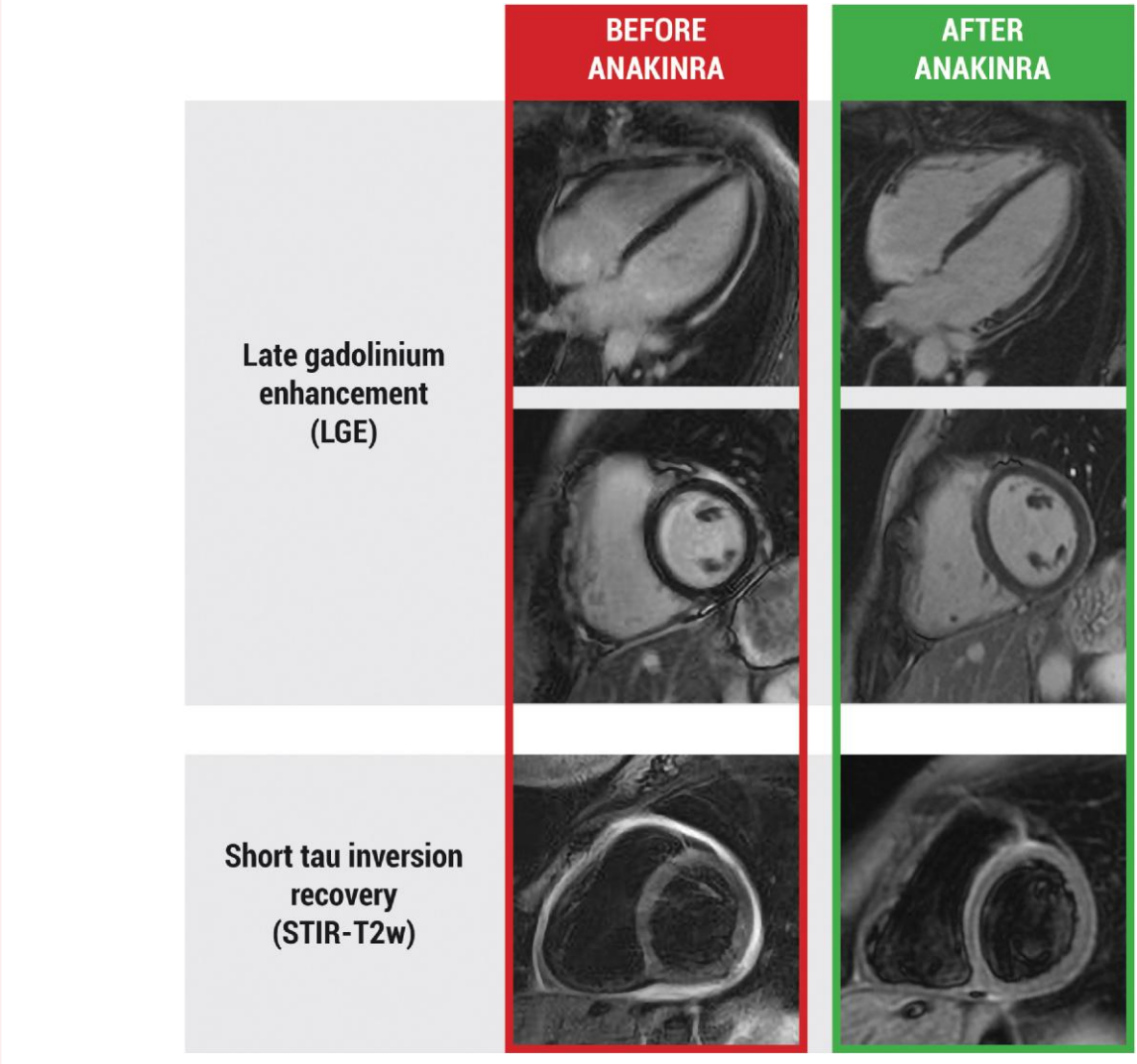


Figure 1 Cardiac magnetic resonance imaging showing significant regression of pericardial inflammation, with minimal residual pericardial late gadolinium enhancement (LGE) and no evidence of oedema on short tau inversion recovery (STIR-T2w) imaging after anakinra treatment.

revealed a virus-negative fibro-productive pericarditis. Colchicine treatment was continued while ibuprofen was switched to indomethacin 50 mg three times daily. The clinical response was insufficient. As a result, a low-moderate dose of methylprednisolone at 0.4 mg/kg daily was added.

Six months since the first recurrence, after methylprednisolone discontinuation, she experienced the second recurrence with typical chest pain and elevated CRP level of 75 mg/L. Given the multiple recurrences, a potential genetic background was explored. A targeted analysis of 20 genes associated with autoinflammatory diseases revealed a heterozygous variant NM_000234.2 (c.1772T > C, p.Ile591Thr) in the Mediterranean fever (MEFV) gene, which was classified as a variant of yet uncertain clinical significance. Triple therapy with indomethacin, colchicine, and methylprednisolone was restarted. However, the patient developed side effects from steroids therapy, including facial swelling, mood swings, and symptoms of depression. Therefore, during hospitalization tapering of the methylprednisolone was attempted but led to another flare. Treatment with anakinra at full dose of 100 mg once daily via subcutaneous injection was initiated. This resulted in immediate clinical improvement with a marked reduction in symptom severity and CRP normalization and allowed methylprednisolone discontinuation.

After 6 months, initial dose of anakinra was slowly tapered by omitting one 100 mg dose per week every month. The patient's condition remained stable on a maintenance regimen of anakinra 100 mg twice weekly and colchicine 0.5 mg once daily.

However, multiple attempts to discontinue anakinra after 2, 3, and 4 years of treatment were unsuccessful as recurrent symptoms and elevated CRP levels developed upon each attempt. During subsequent follow-up, the patient experienced two mild flares: one following messenger ribonucleic acid (mRNA) vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the other during a SARS-CoV-2 infection. Both episodes were successfully treated with transiently increasing the dose of anakinra to 100 mg daily for 1 week. A follow-up cardiac MRI performed 5 years after the initial presentation showed a mildly thickened pericardium and a significant decrease in inflammation, with only remnant pericardial LGE and no oedema visible on STIR-T2w imaging (*Figure 1*). Due to the apparent dependence on anakinra, the presence of neutralizing anti-IL-1Ra antibodies was assessed using an in-house enzyme-linked immunosorbent assay (ELISA) (L. Thurner, Homburg/Saar, Germany),[5,6] following a 2-week asymptomatic anakinra-free interval. The titre of anti-IL-1Ra antibodies was markedly increased (*Figure 2*).

Six months after the last cardiac MRI, she conceived spontaneously. Given her medical history, a multidisciplinary team including a cardiologist, gynaecologist, rheumatologist, and clinical geneticist, all agreed that continued therapy with anakinra was necessary. She was treated with anakinra at a dose of 100 mg twice weekly, but colchicine was discontinued due to gastric problems. Throughout the entire pregnancy, she was closely monitored at the clinic for high-risk pregnancies and cardiology outpatient clinic. Foetal development was carefully monitored with regular ultrasound examinations at weeks 13 (early foetal morphology with nuchal translucency measurement), 18, 20 (foetal morphology), 26, 30, 33, 35, 36, and 39. One month before delivery she complained of mild chest pain with no CRP elevation. Consequently, the anakinra dose was temporarily increased to 100 mg three times weekly until delivery. Foetal growth was appropriate for gestational age until it began to slow after 38 weeks (*Figure 3*). At 39 weeks and 6 days of gestation, just one day before the expected delivery date, labour was induced using local prostaglandin, and the patient delivered a healthy male vaginally. At birth, the baby weighed 2980 g, measured 51 cm in length, had a head circumference of 34 cm, and achieved an APGAR score of 9 at both the first and fifth minutes. The patient continued anakinra treatment at a dose of 100 mg twice weekly during breastfeeding for 12 months and is still following this regimen. The child's growth and development are normal.

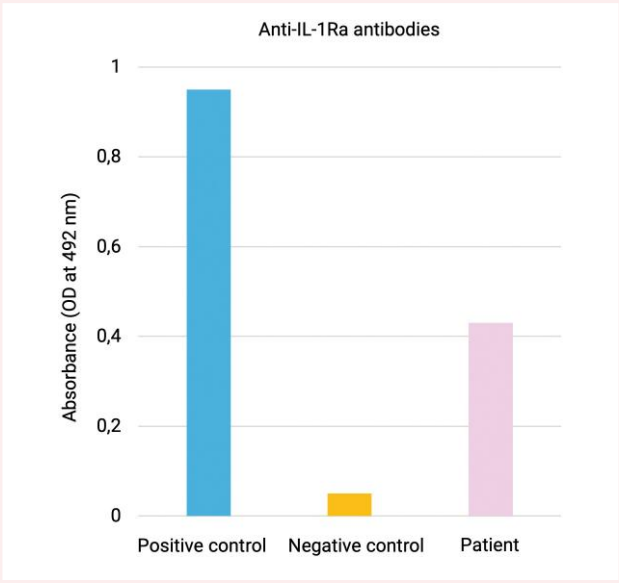


Figure 2 Anti-IL-1Ra antibodies in patient's plasma detected by in-house ELISA (L. Thurner, Homburg/Saar, Germany) were markedly increased. OD, optical density.

Discussion

Our case contributes to the growing evidence supporting the safety of continuous anakinra treatment during pregnancy and lactation in a patient with corticosteroid-dependent, colchicine-resistant recurrent pericarditis. Due to the presence of anti-IL-1Ra antibodies, our patient could not discontinue anakinra and remained on the medication from pre-conception through pregnancy and breastfeeding, without any adverse effects on foetal development or the child's health.

Recurrent pericarditis is believed to be an infectious or immune-mediated condition. In our patient, a comprehensive diagnostic work-up including pericardial biopsy excluded infectious causes of the disease. Immune-related causes can vary from entirely autoinflammatory to entirely autoimmune diseases though the aetiology may involve a combination of both.[2] Inflammatory response of the innate immune system is predominantly mediated by cytokines whereas the inflammatory response of the adaptive immune system is predominantly mediated by autoantibodies or autoreactive T lymphocytes. In our patient, the history of coeliac disease, autoimmune thyroiditis, and the presence of high ANA titres suggested an autoimmune origin. However, relapsing course of the disease with fever, elevated CRP levels, polyserositis and rapid response to IL-1 inhibition were more indicative of autoinflammatory pathogenesis. Recently, recurrent pericarditis with inflammatory phenotype has been attributed to excessive production of IL-1 due to dysregulated activation of the NLRP3 inflammasome.[2]

Genetic polymorphisms in genes encoding innate immune system may contribute to some recurrent pericarditis cases. Genetic variants in MEFV gene, primarily associated with familial Mediterranean fever, have been detected in idiopathic recurrent pericarditis. Recently, the potential pathogenicity of the homozygous R202Q variant in the MEFV gene in recurrent pericarditis has been described.[3] Other, still unknown mutations may also be present. In our patient, a comprehensive exome analysis for periodic fever syndromes identified a heterozygous variant NM_000234.2 (c.1772T > C, p.Ile591Thr) in the MEFV gene, with yet uncertain clinical significance.

Managing recurrent pericarditis resistant to conventional therapies is challenging.[4] Our patient had recurrences despite treatment with a

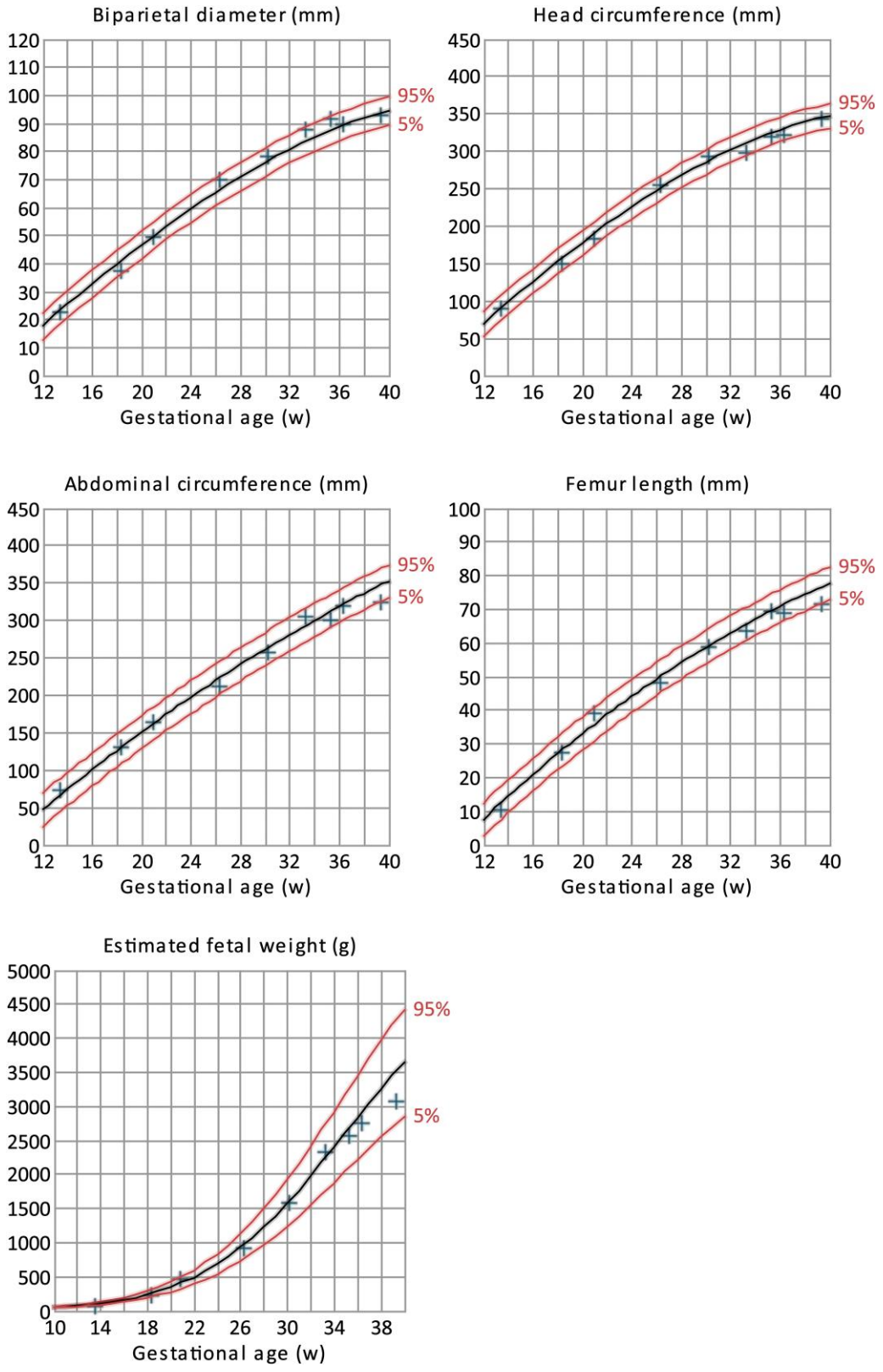


Figure 3 Foetal growth according to ultrasound examinations was consistent with gestational age until it began to slow down after 38 weeks.

combination of different NSAIDs, colchicine, and corticosteroids, with worsening symptoms when corticosteroids was reduced below a critical threshold. This condition is referred to as corticosteroid-dependent and colchicine-resistant recurrent pericarditis. Anakinra, a recombinant human IL-1Ra that inhibits binding of IL-1β to the IL-1 receptor, is a guideline-recommended therapeutic option in these patients.[1] Its effectiveness was confirmed in a randomized clinical trial and an international registry.[7,8] In our patient, introducing anakinra resulted in immediate clinical improvement and allowed corticosteroid withdrawal. However, attempts to discontinue anakinra failed despite various tapering protocols. The development of neutralizing anti-IL-1Ra antibodies might explain this phenomenon. These autoantibodies impair endogenous and recombinant human IL-1Ra-dependent inhibition of IL-1β signalling and may promote inflammatory state. It has been shown that a high proportion of patients (79%) treated with anakinra for cryopyrin-associated periodic syndromes developed anti-drug antibodies within 3 months.[9] The antibody titres subsided subsequently and had no impact on drug efficiency. However, anti-IL-1Ra antibodies detected in our patient are the same as reported in context of multisystem inflammatory syndrome in children or myocarditis linked with mRNA vaccination against SARS-CoV-2 and are unlikely to relate to an anti-drug phenomenon, as none of the individuals tested in these studies has been exposed to anakinra prior to antibody testing.[5,6] Instead, these antibodies likely arise in course of a transient break in peripheral immune tolerance towards endogenous IL-1Ra due to specific post-translational modifications.[5,6] Whether or not these autoantibodies may provide clinically useful biomarkers of anakinra dependency or non-invasive tools to tailor immunosuppressive treatment warrants future assessment.

Women with autoinflammatory diseases face a higher risk of pregnancy complications due to the systemic impact of inflammation. Ideally, remission in autoinflammatory diseases should be achieved at least 6 months prior to conception.[10] In recurrent pericarditis, clinical diagnosis of remission is challenging. Cardiac MRI is effective in assessing pericardial inflammation by detecting pericardial thickening, effusion, oedema/inflammation on STIR-T2w, and inflammation or fibrosis on LGE.[11] The combination of increased STIR-T2w signal and prominent pericardial LGE is consistent with active pericardial inflammation, whereas pericardial LGE in the setting of normal pericardial STIR-T2w signal suggests a subacute process.[12] In our patient, cardiac MRI confirmed disease remission prior to conception, showing substantial regression of pericardial inflammation, as evidenced by minimal residual LGE and the absence of oedema on STIR-T2w imaging.

During pregnancy, the immune system undergoes various adjustments to ensure the foetus is not rejected, which can also affect the course of autoimmune diseases. Some autoimmune diseases tend to improve during pregnancy while others may worsen or remain unchanged. There are at least two mechanisms for overcoming immune reactions during pregnancy including active immunosuppression with decrease in pro-inflammatory cytokines and enhanced tolerance with increased cluster of differentiation (CD)25+ CD4 + regulatory T cells. IL-1β and IL-1Ra appear to play a key role in implantation and placenta development.[13] IL-1Ra regulates IL-1β activity and has been implicated in pregnancy and parturition. In pregnant women, serum IL-1Ra levels increase, while IL-1β levels decrease as gestational age advances. The IL-1 system also plays a role in the initiation of parturition, as it may mediate the pro-inflammatory state that induces spontaneous labour.

Management of complicated recurrent pericarditis in pregnancy and breastfeeding requires personalized approach by weighting the risk-benefit profile of therapeutic options. NSAIDs treatment is allowed up to 20 weeks of gestation, while colchicine and corticosteroids, at the lowest effective dose, can be used throughout pregnancy.[14] Due to limited data on the safety of anakinra there is only low-grade evidence supporting its use during pregnancy and breastfeeding. The European League Against Rheumatism guidelines suggest that anakinra may be tolerated in early pregnancy and can be continued if no alternative treatments are available.[14]

Most of the data on anakinra during pregnancy and lactation come from patients with rheumatic diseases or other immune-mediated conditions, which often have negative impact on fertility and pregnancy. Only individual case reports and analyses of small patient groups who received daily subcutaneous injections of 100 mg anakinra throughout their pregnancies have been published. Two cases of foetal renal malformations have been described, but it remains unclear whether these were directly related to IL-1 pathway inhibition or uncontrolled maternal disease.[15,16] Additionally, a small registry reported two cases of oligohydramnios, which could be associated with uncontrolled maternal hyperthermia.[17] A recent meta-analysis of 69 pregnancies exposed to anakinra, mainly for rheumatic or other immune-mediated conditions, found that the risk of major congenital malformations and miscarriages was comparable to that of the general population.[18] Lack of well-controlled studies make data on the use of anakinra in pregnancy difficult to interpret.

In two recent cases of corticosteroid-dependent, colchicine-resistant recurrent pericarditis, anakinra was discontinued during pregnancy but resumed in the second month due to recurrence. The dose was temporarily increased to 100 mg daily for 1 month, with no reported foetal adverse effects.[19,20] One case resulted in a full-term twin birth, while the other resulted in a pre-term birth at 34 weeks gestation. Unlike previous cases, our patient's treatment was guided by the presence of anti-IL-Ra antibodies, leading to continuous anakinra therapy at 100 mg twice weekly throughout pregnancy. The foetal development was closely monitored with ultrasound examinations including an additional morphology scan at 20 weeks gestation, which showed normal results. One month before delivery, our patient complained of mild chest pain without an elevation in serum inflammatory markers. This symptom may have coincided with the pro-inflammatory shift that occurs towards the end of pregnancy. However, we did not assess the plasma levels of IL-1β and IL-1Ra during pregnancy. Increasing the anakinra dose to 100 mg three times weekly resulted in complete symptom resolution. Labour was induced at 39 weeks/6 days, one day before the expected date.

Since pericarditis flares may occur post-partum, we maintained the increased dose of anakinra for 1 month after childbirth before transitioning back to the maintenance dose. There is no available data on the transfer of IL-1 inhibitors into breast milk. However, since endogenous IL-1Ra is a normal component of human milk, it is unlikely that anakinra would have a significant clinical impact on a breastfeeding infant.[14] In our case, the baby was breastfed for a year with no reported infections or developmental abnormalities. Our patient remained asymptomatic throughout lactation, and subsequent follow-ups.

Conclusion

Managing corticosteroid-dependent, colchicine-resistant recurrent pericarditis during pregnancy requires a personalized approach, ideally with disease stability before conception. Cardiac MRI can accurately evaluate the grade of pericardial inflammation and help guide treatment decisions. In cases of recurrent pericarditis with an inflammatory phenotype, genetic testing for periodic fever syndromes should be performed. Additionally, searching for neutralizing anti-IL-1Ra antibodies may be considered when anti-IL-1 therapies cannot be discontinued. Whether these autoantibodies could serve as clinically useful biomarkers for anakinra dependency or as tools for personalizing immunosuppressive treatment warrants future investigation.

The risks of sub-optimal treatment must be carefully weighed against the potential effects of drug exposure on foetal development; therefore a patient-centred counselling and a multidisciplinary approach are crucial for optimal outcomes. Anakinra may be continued during

pregnancy and lactation in selected patients when no other treatment options are available.

Lead author biography

Andreja Cerne Cercek, MD PhD is an attending cardiologist at the University Medical Centre Ljubljana, Slovenia. Her clinical activity is mostly dedicated to cardiovascular imaging, myocardial and pericardial disease. Her research activity has been focused on myocarditis and pericarditis. She is a member of Slovenian Society of Cardiology, European Society of Cardiology and Working group of Myocardial and Pericardial diseases. She has obtained EACVI certification for transthoracic and transesophageal echocardiography and level III for cardiac MRI.

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Data availability

Non-identifiable data underlying this article will be made available upon reasonable request to the corresponding author.

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