

Idiopathic recurrent pericarditis treated successfully with tumour necrosis factor alpha blocking agents (anti-TNF- α)

J.C. Nieto González¹
I. Monteagudo Saez^{1,2}
F.J. López-Longo¹, B. Serrano¹
C. Mata Martínez¹
L. Carreño Pérez¹

¹Department of Rheumatology and
²Paediatric Rheumatology Unit, Hospital
Gregorio Marañón, Madrid, Spain.

Juan Carlo Nieto González, MD
Indalecio Monteagudo, MD
Francisco Javier López-Longo, MD, PhD
Belén Serrano, MD
Carmen Mata, MD
Luis Carreño, MD, PhD

Please address correspondence to:

Dr Juan Carlos Nieto,
H.G.U. Gregorio Marañón,
Doctor Esquerdo 49,
28007 Madrid, Spain.

E-mail: juanky846@hotmail.com

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ABSTRACT

Idiopathic recurrent pericarditis (IRP) is defined by 2 or more episodes of acute pericarditis of unknown etiology. Either auto-immune or auto-inflammatory diseases are suspected. Usually, non-steroidal anti-inflammatory drugs, colchicine or low dose steroid treatments are effective, however, side effects and/or non-response patients are frequent. We report on three paediatric patients with IRP from our paediatric rheumatology unit. The patients were non-responders to standard therapy and were treated with tumour necrosis factor alpha blocking agents (anti-TNF- α) and showed significant improvement. In two patients, the treatment was tapered and then stopped following several years of therapy. Symptoms flared in the last patient when therapy was tapered more quickly. We conclude that anti-TNF- α can be useful in selected cases of IRP.

Introduction

Recurrent pericarditis is defined by 2 or more episodes of acute pericarditis. RP occurs in 10–30% patients who experience an acute pericarditic event. Most cases are idiopathic. The incidence and prevalence of idiopathic recurrent pericarditis (IRP) are unknown. The pathogenesis is unclear, however, an immune disorder is suspected in most cases, *i.e.* autoimmune (1–3) or auto-inflammatory (4, 5). In nearly 30% of patients the origin is either chronic viral or new viral infection (6).

Clinical manifestations include fever, chest pain, pericardial rub, electrocardiographic (EKG) changes including widespread upward concave ST-segment elevation and PR-segment depression, elevated acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and/or pericardial effusion.

Treatment is not standardised, and includes non-steroidal anti-inflammatory (NSAID) drugs, colchicine, steroids, immunosuppressive agents (azathioprine, methotrexate, cyclosporine A and cyclophosphamide). Intravenous immunoglobulins have been occasionally used (7). Only one case of treatment with etanercept has been reported:

a patient with psoriatic arthritis and recurrent pericarditis (8). One report demonstrated good clinical response with anakinra in 3 paediatric patients with IRP (5).

IRP prognosis is good with no patient record of constrictive pericarditis or left ventricular dysfunction and only a low incidence (3.5%) of cardiac tamponade (9). Despite this, IRP can limit a normal life.

The aim of this report is to document evidence of successful treatment with tumour necrosis factor alpha blocking agents (anti-TNF- α), of three paediatric patients with IRP, in the paediatric rheumatology unit of Gregorio Marañón, Madrid, refractory to standard therapy.

Case reports

Patient 1

A 9-year-old boy, weighing 23 kg, seen in our outpatient unit for right knee monoarthritis and recurrent abdominal pain. In February 2001, he underwent an episode of acute pericarditis consisting of chest pain, dyspnea, an increase of acute phase reactants, EKG abnormalities and moderate pericardial effusion. Infections and autoimmune diseases were ruled out. Familiar Mediterranean Fever (FMF) gene analysis was made in Hospital Clinic, Barcelona. Exon 1 to exon 10 of chromosome 16 were amplified and were normal in February 2003. Exon 2 to exon 5 of TNFRSF1A-associated periodic syndrome (TRAPS syndrome) gene and exon 3 of NLRP3 gene were also tested and negative. An indometacin (100–200 mg/day), colchicine (1 mg/day) and prednisone (1 mg/kg/day) treatment were initiated with no remission of chest pain. Methotrexate was given (7.5 mg weekly) one month later owing to monoarthritis in the past. There was no clinical response at cardiological level and treatment was stopped 4 months later.

During the course of the following 2 years, the boy suffered several episodes of pericarditis (one requiring a pericardiocentesis of 400 ml for severe pericardial effusion) each of which responded to high steroid doses. He received continuous treatment of Ibuprofen (1800 mg/day) and prednisone

Competing interests: none declared.

at high doses (0.5–1 mg/kg/day) during this period. He subsequently developed severe Cushing syndrome and growth retardation. During an acute phase in May 2003, treatment with etanercept was started at standard dosage (25 mg every 4 days), prior consent being given for off-label use. In a few weeks, the patient was asymptomatic. Over the following 7 months, steroids were first tapered and then stopped. Etanercept was administered in monotherapy for 6 months and was then tapered slowly and finally stopped 5 years later. He is now asymptomatic following 3 years without treatment.

Patient 2

An 11-year-old girl, weighing 31 kg, who had no relevant medical history. In May 2006, after the measles, mumps, and rubella (MMR) vaccination, she underwent an acute pericarditis event consisting of chest pain, fever, dyspnea, sternoclavicular and temporo-mandibular bilateral arthritis, elevated acute phase reactants, EKG abnormalities and severe pericardial effusion on echocardiography. Pericardiocentesis was performed, extracting 500 ml of pericardial fluid. Serologies for cytomegalovirus (CMV), Epstein Barr virus (EBV) and Parvovirus B19 and Mantoux were negative. Antinuclear antibodies (ANA), rheumatoid factor (RF) and anti-double stranded DNA (anti-ds-DNA) were negative too. She responded well to NSAID (indometacine 100 mg/day) and prednisone 30 mg daily (0.5–1 mg/kg). When steroids were tapered to 15 mg daily (<0.5 mg/kg), she had another episode of acute pericarditis. She was treated with NSAID (ibuprofen 1800–2400 mg/day) and a further high dosage of steroids. In the following 4-month period, whenever the steroids were tapered below 20–30 mg daily, she suffered a recurrence of acute pericarditis. In the same period, firstly colchicine and then azathioprine were administered in doses of 1 mg/day and 75 mg/day respectively. In both instances, there was no evidence of clinical response. The girl developed a secondary Cushing's syndrome. In October 2006, the girl suffered a further attack of pericarditis. Besides

standard steroidal treatment, we also began a course of etanercept, off label. She responded quite well to etanercept. Between October 2006 and May 2007, we tapered and withdrew the azathioprine and the steroids. The tapering process was repeated with etanercept until the treatment was stopped completely in October 2011. She is asymptomatic after more than 1 year without therapy.

Patient 3

A 14-year-old boy, weighing 63 kg, with no relevant medical history. In August 2008, after a tetanus vaccination, he suffered the onset of chest pain and fever, registered an increase of acute phase reactants and elevated myocardial enzymes, and had typical EKG changes. He was diagnosed with acute myopericarditis and treated with NSAIDs (ibuprofen 1800 mg/day). In 3 months he underwent 3 subsequent episodes of pericarditis, was treated with NSAIDs (ibuprofen 1800 mg/day) and colchicine (1 mg/day) with no subsequent clinical response. No pericardial effusion or enzyme abnormalities were reported following the first episode. ANA, RF, anti-ENA and anti-DNA tested negative. EBV immunoglobulin G tested positive in the first episode. During an acute attack in June 2009, etanercept was given at standard dosage. He improved steadily over the next few weeks before NSAIDs and colchicine were gradually reduced and completely withdrawn 8 months later. The etanercept treatment was tapered in July 2010 until he underwent a recurrent attack in February 2011 for which he was treated with etanercept at the original dosage as well as NSAIDs and colchicine. Despite these modifications, the patient did not improve. In March 2011, adalimumab 40 mg every other week was administered, along with NSAIDs and colchicine. After a few days the patient improved. NSAIDs and colchicine were tapered and finally stopped in June 2011. Clinical response was good in monotherapy until January 2012, when the patient experienced chest pain as an end-of-dose effect. Adalimumab was increased at the dosage of 40 mg every 12 days which re-

sulted in rapid clinical improvement. Currently, the patient is clinically stable on the standard dosage.

Discussion

Herein we describe a successful anti-TNF- α treatment in 3 paediatric patients with IRP. The 2004 international guidelines on the diagnosis and management of pericardial diseases include recommendations on the management of recurrent pericarditis (10). Some controversial points were analysed some years later, but no specific treatment guidelines are available for recurrent pericarditis (11). The standard treatment for pericarditis is high dose NSAIDs and colchicine in the event of recurrence (12). High dose steroids were used to treat recurrences, however, a recent publication showed that low dose steroids have better results (13). Immunosuppressants, such as methotrexate, azathioprine or cyclophosphamide, can be used in severe cases, however, there is no solid evidence. Other treatments were used in isolated cases (5, 7, 8). Although the standard treatment of pericarditis is usually enough to control symptoms, however this produces side effects frequently and not all patients respond. Avoiding these side effects is important, even more so in children.

IRP is a heterogeneous disease in which an immunologic disorder in most cases is every day more accepted. IRP had been associated with autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, psoriatic arthritis, rheumatic polymyalgia, scleroderma, Behçet's disease, polymyositis, dermatomyositis, systemic vasculitis and giant cell temporal arteritis), with autoinflammatory diseases (FMF and TNFRSF1A-associated periodic syndrome syndrome (TRAPS)) and viral infections (chronic or viral reinfection).

Autoimmune disorder is supported by ANA and cardiac-specific antibodies positivity in IRP patients (2, 3). ANAs were present in 43.4% of patients affected by IRP, at low titers in the majority of cases (<1/160), in respect to 9.8% in healthy controls. Patients who had moderate or high titers of ANA ($\geq 1/160$) developed more frequently a

specific autoimmune disease (6.6% in the follow-up) (2).

Specific cardiac antibodies were associated with IRP. Anti-heart antibodies (AHA) and anti-intercalated disk autoantibodies (AIDA) were positives in 50% and 25% respectively, compared with non-inflammatory cardiac diseases (4% and 4%), ischaemic heart failure (1% and 2%) and normal subjects (3% and 0%). AHA and/or AIDA were found in 67.5% of patients with IRP (3). Autoinflammatory diseases such as FMF, hyper-IgD syndrome (HIDS) or TRAPS syndrome can produce recurrent pericarditis (14-16). IL-1 receptor antagonist (anakinra), useful in autoinflammatory diseases could also be useful in IRP (5).

In a recent paper, the systematic research of mutation of TNFRSF1A in 131 IRP patients showed a high prevalence of low penetrance mutation R92Q in patients (6.1%) in respect to healthy controls (2.5-4%). Even if the pathogenic impact of low penetrance of TNFRSF1A is still a matter of debate, this group recommended testing for TRAPS syndrome in patients with IRP who do not respond to colchicine (14). One patient was reported with HIDS in treatment with etanercept, with good clinical response, but developed IRP (15). Even if the association between pericarditis and FMF is well known (16), no mutations in the FMF gene were found in one large cohort of 23 IPR patients (17).

None of our patients had had periodic fever and all responded well to anti-TNF- α ; On the other hand, we did not perform the genetic analysis for TRAPS syndrome, HIDS syndrome or FMF in all our patients, and we can not exclude some autoinflammatory diseases. The first 2 patients had a good

clinical response and the therapy was tapered slowly and stopped following long-term treatment, the relapse in the third patient could be related to faster tapering of the treatment, necessitating a slow taper and a long-term treatment to control the disease.

Our patients were treated with NSAID and colchicine, standard treatment of pericarditis, but usually the NSAID dosage was low or insufficient. The doses of NSAID might have been increased in our patients.

Therefore, IRP is a clinical manifestation of many diseases, either autoimmune, autoinflammatory or infectious. Standard treatment works in the majority of cases, but side effects are frequent. Anti-TNF- α could be a therapeutic option in some specific patients with IRP, and can be tapered and stopped in some cases maintaining remission.

References

1. NOEL R: Recurrent pericarditis: an autoimmune disease? *Heart* 2010; 96: 734-35.
2. IMAZIO M, BRUCATO A, DORIA A *et al.*: Antinuclear antibodies in recurrent idiopathic pericarditis: Prevalence and clinical significance. *Intern J Cardiol* 2008; 136: 289-93.
3. CAFORIO A, BRUCATO A, DORIA A *et al.*: Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. *Heart* 2010; 96: 779-84.
4. CANTARINI L, IMAZIO M, BRUCATO A, LUCHERINI OM, GALEAZZI M: Innate versus acquired immune response in the pathogenesis of recurrent idiopathic pericarditis. *Autoimmun Rev* 2010; 9: 436-40.
5. PICCO P, BRISCA G, TRAVERSO F, LOY A, GATTORNO M, MARTINI A: Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1 receptor antagonist (Anakinra). *Arthritis Rheum* 2009; 60: 264-68.
6. BRUCATO A, MAESTRONI S, CUMETTI D *et al.*: Recurrent pericarditis: infectious or autoimmune? *Autoimmun Rev* 2008; 8: 171-77.
7. TONA F, BELLOTTO F, LAVEDER F, MENEGHIN A, SINAGRA G, MARCOLONGO R: Efficacy of high-dose intravenous immunoglobulins in two patients with idiopathic recurrent pericarditis refractory to previous immunosuppressive treatment. *Heart* 2003; 4: 64-68.
8. ESPOSITO M, GIUNTA A, BABINO G, SCHIPANI C, MARCHEI M, CHIMENTI MS: Resolution of idiopathic recurrent pericarditis in a psoriatic arthritis patient treated with etanercept. *Eur J Dermatol* 2012; 22: 151-2.
9. IMAZIO M, BRUCATO A, ADLER Y *et al.*: Prognosis of idiopathic recurrent pericarditis as determined from previously published reports. *Am J Cardiol* 2007; 100: 1026-28.
10. MAISCH B, SEFEROVIC PM, RISTIC AD *et al.*: Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. Guidelines on the Diagnosis and Management of Pericardial Diseases. *Eur Heart J* 2004; 25: 587-610.
11. IMAZIO M, SPODICK DH, BRUCATO A, TRINCHERO R, ADLER Y: Controversial issues in the management of pericardial diseases. *Circulation* 2010; 121: 916-28.
12. IMAZIO M, BRUCATO A, CEMIN R *et al.*, ON BEHALF OF THE CORP (COLCHICINE FOR RECURRENT PERICARDITIS) INVESTIGATORS: Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med* 2011; 155: 409-14.
13. IMAZIO M, BRUCATO A, CUMETTI D *et al.*: Corticosteroids for recurrent pericarditis: high versus low doses. A non-randomized observation. *Circulation* 2008; 118: 667-71.
14. CANTARINI L, LUCHERINI OM, BRUCATO A *et al.*: Clues to detect tumour necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. *Clin Res Cardiol* 2012; 101: 525-31.
15. BREDA L, NOZZI M, DI MARZIO D, DE SANTIS S, GATTORNO M, CHIARELLI F: Recurrent pericarditis in hyper-IgD syndrome. *Clin Exp Rheumatol* 2009; 27: 695.
16. DABESTANI A, NOBLE LM, CHILD JS, KRIVOKAPICH J, SCHWABE AD: Pericardial disease in familial Mediterranean fever: an echocardiographic study. *Chest* 1982; 81: 592-95.
17. BRUCATO A, SHINAR Y, BRAMBILLA G *et al.*: Idiopathic recurrent acute pericarditis: familial Mediterranean fever mutations and disease evolution in a large cohort of Caucasian patients. *Lupus* 2005; 14: 670-74.