Efficacy of high-dose intravenous immunoglobulins in two patients with idiopathic recurrent pericarditis refractory to previous immunosuppressive treatment

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Although idiopathic acute pericarditis is usually a self-limiting disease, in many patients it may recur over a period of months or years. Even if some evidence seems to suggest the possible role of a deranged immune reactivity in the pathogenesis of idiopathic recurrent pericarditis, the etiology of the disease is still unknown. Furthermore, while some trial data confirm the usefulness of colchicine, its medical treatment is not yet clearly established.

We here report the clinical history of 2 patients with idiopathic recurrent pericarditis resistant to prednisone, colchicine and other immunosuppressive drugs, who have been successfully treated with high-dose intravenous immunoglobulins.

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Introduction

Idiopathic acute pericarditis is usually a self-limiting disease with a good prognosis[1]. However, 15 to 32% of patients suffer from repeated episodes of the disease with chest pain, fever and typical ECG signs, with or without pericardial effusion, over a period of months or years[2].

The etiology of idiopathic recurrent pericarditis is still unknown, even though clinical and histologic evidence suggests the possible crucial role of a deranged local immune response[3-5].

To date, the optimal medical treatment for idiopathic recurrent pericarditis has not yet been clearly established. Actually, regardless of the usual good clinical response to conventional corticosteroid therapy, the disease frequently recurs following its discontinuation. Yet, while some trial data confirm the usefulness of colchicine in adjunct to the conventional treatment for idiopathic recurrent pericarditis, so far the reported efficacy of high-dose corticosteroids and immunosuppressive agents has not been tested in specific clinical studies[3-5].

Although high-dose intravenous immunoglobulins (HD-IVIg) have been reported to be effective for the treatment of several autoimmune or immune-mediated diseases, the mechanism by which they exert their clinical effect appears to be quite complex and still not completely understood[6,7].

We here report the clinical history of 2 patients with idiopathic recurrent pericarditis resistant to non-steroidal anti-inflammatory drugs (NSAIDs), prednisone, colchicine and other immunosuppressive drugs, who have been successfully treated with HD-IVIg.

Description of cases

Case 1. A 30-year-old man was admitted to our hospital in March 1998 with recurrent pericarditis. Five years earlier he had been admitted to another hospital for the first time because of the gradual onset of chest pain following a flu-like episode. The patient completely recovered following a short course of antibiotics and antipyretics. However, 3 months later he again began to complain of the same symptoms which, on the basis of an ECG and of echocardiographic evaluation, were interpreted as a relapse of the disease. Microbiological tests on the pharyngeal smear, sputum, urine and blood were negative; an intradermal test for tuberculin and chest X-rays were negative; the serum circulating im-

mune complexes rheumatoid arthritis test, antinuclear, anti-DNA, antimitochondrial, antismooth muscle, antigastric parietal cells, antimicrosomal, antithyroglobulin, anticardiolipin antibodies, venereal disease research laboratory and phenotype were negative or within the normal range. An ECG showed sinus tachycardia (115 b/min) and widespread ST-segment elevation and echocardiography revealed a pericardial effusion (800 ml) confirming the diagnosis of idiopathic recurrent pericarditis. At first, the patient showed a good clinical response to aspirin (4-6 g/day), but he presented with new disease recurrence at every attempt to discontinue the therapy. For this reason, oral prednisone (75 mg/day) was started, but 2 months following the decrease in dosage to below 30 mg/day, the patient presented with cardiac tamponade necessitating pericardiocentesis. The adjunct of colchicine (1 mg/day for 3 months) did not change the situation. Further therapeutic attempts with prednisone (75 mg/day), at first in combination with azathioprine (150 mg/day for 2 months) and then with cyclosporin A (300 mg/day for 6 months), did not prevent the recurrence of the disease. Cyclophosphamide (100 mg/day) in combination with oral prednisone (40 mg/day) determined a transient clinical remission (6 months), but, once again, when prednisone was tapered below 10 mg/day a new relapse occurred. Meanwhile the patient developed severe hypercortisolism (Table I).

In 1997, the patient underwent surgery to open a pleural-pericardial window. The pericardial biopsy showed a widespread thickening of the pericardial wall together with a non-specific perivascular infiltration of lymphocytes and macrophages. Pericardial fluid and tissue cultures were negative for mycobacteria.

The patient was then referred to our hospital where secondary causes of pericarditis were carefully ruled out and the diagnosis of idiopathic recurrent pericarditis confirmed. After informed consent, the patient agreed to undergo HD-IVIg therapy in the attempt to stop the vicious circle and to escape steroid dependence. Prednisone was then gradually discontinued. As soon as the symptoms of pericarditis reappeared (fever and chest pain along with tachycardia, other typical ECG signs and an estimated pericardial effusion of about 600 ml), the patient was submitted to HD-IVIg therapy (Ig VENA N, Farma Biagini SpA, Castelvecchio Pascoli-LU, Italy), 500 mg/kg/day for 5 days. On the third day of infusion, the fever disappeared and chest pain began to decrease, the patient's clinical conditions gradually improved and acetaminophen administration was stopped; the ECG signs progressively faded despite the persistence of pericardial effusion (average 600-800 ml) and of increased erythrosedimentation rate (110 mm/hour). He did not experience any adverse effect related to the treatment and, despite a weight loss of about 6 kg and a lasting sensation of fatigue, he could leave the hospital after 3 weeks on a small oral dose of indomethacin (50 mg/day), which he discontinued within 2 weeks. After 1 month, the inflammatory indexes, ECG and chest X-ray were completely normalized, while echocardiography revealed a persistent pericardial effusion of about 200-300 ml that completely disappeared within 3 months. During a follow-up period of 42 months, the patient has been completely free from any sign or symptom of pericarditis and his conditions remained stable without any treatment.

Case 2. A 19-year-old girl was admitted to our hospital in September 1997 with a history of idiopathic recur-

Table I. Inflammatory indexes in the different periods of treatment.

Inflammatory indexes before and after the therapies	Patient 1	Patient 2
ESR (mm/hour) before PDN	100	113
ESR (mm/hour) after PDN	10	14
CRP (mg/l) before PDN	138	72
CRP (mg/l) after PDN	< 6	10
ESR (mm/hour) before PDN + colchicine	113	*
ESR (mm/hour) after PDN + colchicine	21	*
CRP (mg/l) before PDN + colchicine	124	*
CRP (mg/l) after PDN + colchicine	10	*
ESR (mm/hour) before PDN + azathioprine	115	*
ESR (mm/hour) after PDN + azathioprine	15	*
CRP (mg/l) before PDN + azathioprine	198	*
CRP (mg/l) after PDN + azathioprine	< 6	*
ESR (mm/hour) before PDN + cyclosporin	123	111
ESR (mm/hour) after PDN + cyclosporin	18	13
CRP (mg/l) before PDN + cyclosporin	175	121
CRP (mg/l) after PDN + cyclosporin	7	< 6
ESR (mm/hour) before PDN + cyclophosphamide	98	114
ESR (mm/hour) after PDN + cyclophosphamide	13	14
CRP (mg/l) before PDN + cyclophosphamide	176	194
CRP (mg/l) after PDN + cyclophosphamide	< 6	< 6

CRP = C-reactive protein; ESR = erythrosedimentation rate; PDN = prednisone. * therapy not administered.

rent pericarditis. She had been first admitted to another hospital in 1995 because of the sudden onset of pericarditis complicated by cardiac tamponade. She underwent pericardiocentesis and was then placed on steroids (oral prednisone 0.5 mg/kg/day, tapered and discontinued within 45 days) and antibiotics. However, 1 month later, given the persistence of significant pericardial effusion, a pleural-pericardial communication was created. Pericardial biopsy revealed mononuclear cell infiltration (T-lymphocytes, macrophages and plasma cells) with no signs of mycobacterial infection. The addition of colchicine 1 mg/day did not prevent the recurrence of pericarditis when prednisone was tapered to less than 10 mg/day 2 months later. The resumption of a larger (25 mg) daily dosage of prednisone immediately restored full clinical control of the situation until the following month, when a new attempt to taper prednisone below the dose of 15 mg/day induced a new severe relapse. Methylprednisolone (160 mg/day i.v. for 3 days) and then oral prednisone (50 mg/day) were administered achieving the complete resolution of the clinical picture. However, when prednisone was once again tapered below the dose of 12.5 mg/day, after 2 months, a new relapse occurred, requiring an immediate increase in the daily prednisone dosage. Several therapeutic attempts with different immunosuppressive agents (i.v. cyclophosphamide for 3 months, cyclosporin A for 12 months, oral methotrexate for 9 months) in the following 2 years did not prevent the relapses of the disease every time the daily prednisone dose was decreased below 10.5 mg (Table I).

On admission to our hospital, the patient was still taking 10 mg of prednisone per day along with cyclosporin A 300 mg/day and methotrexate 5 mg/day; she presented with evident clinical signs of hypercortisolism and profound emotional changes. As previously described, after informed consent, the patient agreed to undergo HD-IVIg therapy (Ig VENA N, Farma Biagini SpA, Italy), 500 mg/kg/day for 5 days.

Following the gradual discontinuation of the previous treatment, fever, dyspnea and chest pain reappeared along with typical ECG and echographic signs of pericarditis; the erythrosedimentation rate rose up to 120 mm/hour and the serum levels of C-reactive protein up to 58.20 mg/l (normal range < 6 mg/l). On the fourth day of HD-IVIg infusion, chest pain and fever began to spontaneously decrease and completely disappeared within a few days. Echocardiography revealed that pericardial effusion had resolved. After 1 week the chest X-ray was normal as were the inflammatory indexes. The patient did not experience any adverse effect related to the treatment, and after 10 days she was able to leave hospital in good clinical conditions and on oral indomethacin (75 mg/day).

During a follow-up period of 32 months the patient did not experience any further recurrence of pericarditis and her physical conditions remained steadily normal without any treatment.

Discussion

In the 2 patients described here, therapy with HD-IVIg has been associated with the complete and stable resolution of every sign and symptom of pericardial inflammation.

Indeed, given the patients' previous clinical history and the close temporal relationship observed between the HD-IVIg therapy and the clinical response, the possibility of spontaneous remission appears unlikely.

Some evidence suggests that idiopathic recurrent pericarditis, which has been associated with some conditions of hypersensitivity, has an immune pathogenesis[1,3,4]. It has also been suggested that the disease may recur as a consequence of an autoaggression mediated by cytotoxic T-lymphocytes and natural-killer cells[4]. With regard to this, the presence of CD8+ T-lymphocytes has been demonstrated in the pericardial tissue of patients with rheumatoid pericarditis as well as in that of subjects suffering from idiopathic recurrent pericarditis[8]. In addition, some immunological studies provide evidence of a T-lymphocyte autosensitization against cardiac antigens in patients with idiopathic recurrent pericarditis[9]. Finally, the massive pericardial mononuclear cell infiltration (T-lymphocytes, macrophages, plasma cells) found in the 2 cases here discussed strongly supports the hypothesis of an autoimmune disease. However, the putative pericardial antigens that feed the immune reaction thus fuelling an idiopathic recurrent pericarditis vicious circle remain unknown. Consequently, idiopathic recurrent pericarditis could be interpreted as an organ-specific autoimmune disease triggered by different causes such as a virus or other infectious agents, traumatic or ischemic injuries and drugs or toxic agents, and sustained by both cellular (possibly by T helper 1 cells in the exudative forms and by T helper 2 in the fibrous/constrictive forms) and humoral (autoantibody production or immune complex deposition) reactions. The recent demonstration of activation markers and of soluble mediators of inflammation such as interleukin (IL)-6, IL-8 and interferon-gamma in the pericardial effusion of patients with pericarditis, confirms the local release of cytokines by activated T-lymphocytes[5].

In this respect, treatment with NSAIDs or low-dose/short-term steroids, which could initially be effective in controlling pericardial inflammation, may eventually turn out to be inadequate for the definitive inhibition of the apparently self-feeding immune response occurring in idiopathic recurrent pericarditis.

In contrast, clinical data that have been accumulated in the past decade provide evidence for the efficacy and safety of colchicine as an adjunct to conventional treatment for the prevention of idiopathic recurrent pericarditis[10-12]. Immunosuppressive agents, such as methylprednisolone[13], azathioprine[14,15], high-dose prednisone, cyclophosphamide[15] and cyclosporin A[16], are also reported to inhibit and, possibly, to eradicate idio-

pathic recurrent pericarditis, although controlled specific clinical studies are not yet available.

Nevertheless, in the 2 cases here reported neither colchicine nor immunosuppressive agents definitely resolved the recurrence of idiopathic recurrent pericarditis. Therefore, we considered the utilization of different immunosuppressive/immunomodulatory therapeutic approaches such as HD-IVIg. HD-IVIg have already shown their efficacy in the treatment of some critical autoimmune diseases, including systemic lupus erythematosus (SLE)-related pericarditis[17]. The mechanism by which they exert their clinical effect appears to be quite complex and remains to be elucidated. Several non-mutually exclusive mechanisms have been proposed to account for the beneficial immunomodulatory effects of HD-IVIg. These include functional blockade of the Fc receptors on phagocytes, inhibition of the deposition of activated complement components on target cells, modulation of the secretion of cytokines and cytokine antagonists, interference with T and B cell proliferation, neutralization of pathological autoantibodies, and long-term selection of immune repertoires[6,7]. In addition, HD-IVIg probably produce an immunomodulatory action that is different in each disease[18]. In immune thrombocytopenic purpura there is evidence for a blockade of the membrane receptors for the Fc portion of IgG and for an anti-idiotypic modulation of the immune response[19,20]. In Kawasaki's syndrome HD-IVIg seem to modify the production and release of cytokines[21,22]. Intravenous immunoglobulins have been able to "solubilize" immune complexes after *in vitro* incubation in renal tissue sections from SLE patients[23].

Some evidence supports the notion that the diversity of the variable regions in intravenous immunoglobulin preparations is a determining factor for their anti-inflammatory and immunomodulatory action and for the selection of immune repertoires[24]. In addition HD-IVIg can regulate cell proliferation by modulation of Fas-induced apoptosis[24]. Finally, although the major component in HD-IVIg is immunoglobulin G, other minor components such as solubilized lymphocyte surface membrane determinants and specific antibodies to lymphocyte surface molecules may have important immunoregulatory effects both on T and B cell immune responses[25].

The favorable clinical outcome observed in our 2 patients may be the result of pericardial macrophage immunoglobulin-Fc receptor blockade. The consequent inhibition of macrophage activation may reduce the local release of inflammatory monochines (tumor necrosis factor, IL-1 and IL-6). On the other hand, the observed long-term efficacy could be related to an anti-idiotypic modulation of the local immune response or to the induction of apoptosis of autoreactive clones.

Recently, the efficacy of HD-IVIg in the treatment of SLE-related polyserositis has been once more reported[18], but to the best of our knowledge, this is the first report describing the successful use of HD-IVIg in patients with recurrent pericarditis not related to a connective tissue disease. On the basis of this preliminary evidence, we believe that HD-IVIg can be considered as a possible rescue therapy for patients with idiopathic recurrent pericarditis refractory to conventional treatment.

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