Efficacy of High-Dose Intravenous Immunoglobulins in Two Patients with Idiopathic Recurrent Pericarditis Refractory to Previous Immunosuppressive Treatment

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Abstract

Although idiopathic acute pericarditis is usually a self-limiting disease, in many patients it may recurs 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 aetiology 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 two patients with idiopathic recurrent pericarditis, resistant to prednisone, colchicine and other immunosuppressive drugs, who have been successfully treated with high-dose intravenous Immunoglobulins.

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 aetiology of Idiopathic Recurrent Pericarditis (IRP) is still unknown, even if the clinical and histological evidence suggests the possible crucial role of a deranged local immune response [3-5].

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

Although the effectiveness of high-dose intravenous Immunoglobulin (HD-IVIg) therapy has been reported in the treatment of several autoimmune or immune-mediated diseases, the mechanism by which it exerts its clinical effect appears to be quite complex and still not completely understood [6-7].

We here report the clinical history of two patients with IRP, resistant to non steroid antiinflammatory drugs (NSAID), prednisone, colchicine and other immunosuppressive drugs, who have been successfully treated with HD-IVIg.

Case n° 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, three months later he again began to complain of the same symptoms which, on the base of an ECG and echocardiography evaluation, were interpreted as a relapse of the disease. Microbiological tests on pharyngeal smear, sputum, urine and blood were negative; an intradermal test for tuberculin and chest X-rays were negative, serum circulating immune-complexes (CICs), RA-test, antinuclear, anti-DNA, anti-mitochondria, anti-smooth muscle, anti-gastric parietal cells, anti-microsome, anti-thyreoglobulin, anti-cardiolipin antibodies, VDRL and phenotype were negative or within the normal range. An ECG showed sinus tachycardia (115/min) and diffuse ST-segment elevation and echocardiography revealed a pericardial effusion (800 ml) confirming the diagnosis of IRP. At first, the patient showed a good clinical response to aspirin, 4-6 g/day, but he experienced a new disease recurrence at every attempt to discontinue the therapy. For this reason, oral prednisone, 75 mg/day, was started, but, when the drug was tapered to below 30 mg/day a cardiac tamponade occurred that required a pericardiocentesis. The adjunct of colchicine, 1 mg/day for three months, did not change the situation. Further therapeutic attempts with prednisone, 75 mg/day, at first in combination with azathioprine, 150 mg/day, and then with cyclosporin-A, 300 mg/day, did not avoid 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 hypercorticism.

In 1997, the patient underwent surgery to open a pleuro-pericardial window. The pericardial biopsy showed a diffuse thickening of pericardial wall together with a non-specific perivascular infiltration of lymphocytes and macrophages. A search for mycobacteria in both pericardial fluid and tissue was negative

The patient was then referred to our hospital where secondary causes of pericarditis were carefully ruled out and the diagnosis of IRP 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 and completely discontinued. As soon as pericarditis symptoms reappeared (fever and chest pain along with tachycardia, other typical ECG signs and an estimated pericardial effusion of about 600 ml), the patient received HD-IVIg therapy (Ig VENA N, Farma Biagini SpA, Italy), 500 mg/kg/day for five days. At the third day of infusiony, the fever disappeared and chest pain began to decrease, the patient's clinical condition gradually improved and acetaminophen administration was stopped; ECG signs progressively faded despite the persistence of pericardial effusion (average 600-800 ml) and ESR elevation (110 mm). He did not experience any adverse effect from treatment and, despite a weight loss of about six kilograms and a lasting sensation of fatigue, he could leave the hospital after three weeks with a small oral dose of indomethacin, 50 mg/day, which he discontinued within two weeks. After one month, inflammatory indexes, ECG and chest X-ray were completely normalized, while echocardiography revealed a lasting pericardial effusion of about 200-300 ml that completely disappeared within three months. During a follow-up period of 38 months, the patient has been completely free from any sign or symptom of pericarditis and his condition has remained stable without any treatment.

Case n° 2

A 19-year-old girl was admitted to our hospital in September 1997 with a history of IRP. She has been first admitted to another hospital in 1995 with the sudden appearance of pericarditis complicated by heart tamponade. She underwent pericardiocentesis, followed by steroids (oral prednisone 0.5 mg/kg/day, tapered and discontinued in 45 days) and administration of antibiotics. However, a month later, given the persistence of a significant pericardial effusion, a pleural-pericardial communication was created. Pericardial biopsy revealed a mononuclear cell infiltration (T lymphocytes, macrophages and plasma-cells) with no signs of mycobacterial infection. The addition of colchicine, 1 mg/day, did not avoid the recurrence of pericarditis when prednisone was tapered to less than 10 mg/day two months later. The resumption of a larger (25 mg) daily dosage of prednisone immediately restored a 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 pericarditis relapse. Methylprednisolone, 160-mg/day i.v. for three days, and then oral prednisone, 50 mg/day, were administered obtaining the complete resolution of the clinical picture. However, when prednisone was once again tapered below the dose of 12.5 mg/day, a new relapse occurred, requiring an immediate increase of the daily prednisone dosage. Several therapeutic attempts with different immunosuppressive agents (i.v. cyclophosphamide, cyclosporin A, oral methotrexate) in the following two years did not prevent the relapses of the disease every time the daily prednisone dose went below 10-5 mg/day. 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 had visible clinical signs of hypercorticism and her psychological balance was seriously impaired. 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 five days).

Following the gradual discontinuation of previous treatment , fever, dyspnoea and chest pain reappeared along with typical ECG and echographic signs of pericarditis; ESR rose up to 120 mm/h and CRP 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 disappeared within a few days. Echocardiography did not reveal pericardial effusion any longer. After one week chest x-rays and inflammatory indexes returned normal. The patient did not experience any adverse effect from the treatment, and after 10 days she was able to leave hospital in good clinical condition taking indomethacin, 75 mg/day.

During a follow-up period of 28 months the patient did not experience any further recurrence of pericarditis and her physical condition remained steadily normal without any treatment.

Discussion

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

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

Some evidence suggests that IRP, which has been associated with 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 auto-aggression mediated by cytotoxic T-lymphocytes and natural-killer (NK) cells [4]. In this view, the presence of CD8+ T-lymphocytes has been demonstrated in the pericardial tissue of patients with rheumatoid pericarditis as well as in those suffering from IRP [8]. In addition, some immunological studies provide evidence of a T-lymphocyte auto-sensitisation against

cardiac antigens in patients with IRP [9]. Finally, the massive pericardial mononuclear cell infiltration (T lymphocytes, macrophages, plasma-cells) found in the two cases here discussed strongly supports the hypothesis of an autoimmune disease, even if putative pericardial antigens that feed immune reaction fuelling an IRP vicious circle remain unknown. Consequently, IRP could be interpreted as an organ-specific autoimmune disease, triggered by different causes such as a virus or other infectious agents, traumatic or ischaemic injuries, drugs or toxic agents, and sustained by both cellular (possibly by T helper 1 cells in essudative forms and by T helper 2 in fibrosing/constrictive forms) and humoral (auto-antibody production or immune-complex deposition) reactions. The recent demonstration of activation markers and soluble mediators of inflammation such as IL-6, IL-8 and IFN-gamma in pericardial effusion of pericarditis patients confirms the local release of cytokines by activated T lymphocytes [5].

In this view, the treatment with NSAIDs or low dose/short-term steroid, which could be effective at first in controlling pericardial inflammation, may eventually result inadequate to steadily inhibit the apparently self-feeding immune response taking place during IRP.

In contrast, clinical data that have accumulated in the past decade provide evidence for the efficacy and safety of colchicine in addition to conventional treatment for the prevention of IRP [10-12]. Immunosuppressive agents, such as methylprednisolone [13], azathioprine [14-15], high dose prednisone, cyclophosphamide [15] and Cyclosporin A [16], are also reported to produce inhibition and possibly eradication of IRP, although controlled specific clinical studies are not yet available.

Nevertheless, in the two cases reported neither colchicine nor immunosuppressive agents were able to continue to prevent IRP recurrences. Therefore, we took into

account the utilisation 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 SLE-related pericarditis [17]. The mechanism by which they exert their clinical effect appears to be quite complex and remains little understood. Several non-mutually exclusive mechanisms have been proposed to account for the beneficial immunomodulatory effects of HD-IVIg. These include the functional blockade of 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 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 production and release of cytokines [21-22]. IVIg have been able to "solubilize" immune complexes after in vitro incubation in renal tissue section from SLE patients [23].

Some evidence supports the notion that the diversity of V regions in IVIg 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 through modulation of Fas-induced apoptosis [24]. Finally, although the major component in HD-IVIg is IgG, 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 favourable clinical outcome observed in our two patients may be the result of pericardial macrophage Ig-Fc receptor blockade. The consequent inhibition of macrophage activation may reduce local release of inflammatory monochines (TNF, IL-1 and IL-6). Long-term efficacy could be rather related to an anti-idiotypic modulation of local immune response or to the induction of apoptosis of autoreactive clones.

Recently, the efficacy of HD-IVIg has been once more reported in the treatment of SLE-related polyserositis [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 HD IVIg can be considered as a possible rescue therapy for patients with IRP refractory to conventional treatment.

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