Acute myocardial infarction associated with high dose intravenous immunoglobulin infusion for autoimmune disorders. A study of four cases

Ori Elkayam, Daphna Paran, Ronny Milo, Yaron Davidovitz, Dorit Almoznino-Sarafian, David Zeltser, Michael Yaron, Dan Caspi

Abstract

***Objective*—To report on four patients with autoimmune disorders who developed acute myocardial infarction (MI) during or soon after treatment with high dose intravenous immunoglobulins (IVIG) and to determine the clinical profile of patients prone to this complication.**

***Methods*—The clinical history of the four patients is reported with details concerning age, sex, indication for IVIG treatment, risk factors, timing of the MI and outcome. The relevant medical literature has been reviewed.**

***Results*—The patients, three men and one woman, aged 42–67, received IVIG treatment for different autoimmune disorders. All had a history of atherosclerosis or previous risk factors such as hypertension, stroke, hyperlipidaemia and obesity. Two of the patients suffered a MI after the first infusion of IVIG while the others—after the 5th and 15th pulses. MI occurred during the infusion in two patients and after a few days in the others. All the patients recovered from the acute event. These observations are in concert with sporadic cases of IVIG related thrombosis reported in the medical literature.**

***Conclusion*—In patients with vascular risk factors such as old age, hypertension, history of stroke or coronary artery disease, the possibility of IVIG related vascular complications should be considered and IVIG prescribed with a cautious re-weighted risk/benefit consideration.**

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Department of Rheumatology, Tel Aviv "Sourasky" Medical Centre, Israel
O Elkayam
D Paran
M Yaron
D Caspi

Department of Neurology, Assaf Harofeh Medical Centre, Israel
R Milo

Department of Haematology, E Wolfson Medical Centre, Israel
Y Davidovitz

Department of Medicine F, Assaf Harofeh Medical Centre, Israel
D Almoznino-Sarafian

Department of Medicine, Tel Aviv "Sourasky" Medical Centre, Israel
D Zeltser

Correspondence to:
Dr O Elkayam, Department of Rheumatology, Tel Aviv "Sourasky" Medical Centre, 6 Weizman Street, Tel Aviv 64329, Israel.

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High dose intravenous immunoglobulin (IVIG) treatment is being increasingly used in a wide range of autoimmune disorders such as Kawasaki,[1] neuroimmunological disorders,[2–4] dermatomyositis,[5] vasculitis[6] immune cytopenia and other conditions.[7 8] IVIG have been considered a safe medication, with minor adverse events such as headache, nausea and myalgias, occurring in less than 10% of patients.[9 10] With the wider use of IVIG, the reported rate of side effects has increased,[11] some of them being potentially fatal.[12]

We describe four patients with autoimmune disorders who developed acute myocardial infarction (MI) a few days after receiving IVIG.

Case reports

CASE 1

The patient is a 60 year old man with relapsing polychondritis of three years duration manifesting as extreme fatigue, recurrent episodes of chondritis of the ears, hoarseness, livedo reticularis, migratory arthritis and myalgias, episcleritis and vestibular neuropathy with vertigo and sensorineural deafness. He had documented arterial hypertension for the past two years. Laboratory tests disclosed an increased erythrocyte sedimentation rate (ESR) (120 mm 1st h) and normocytic normochromic anaemia (Hb 10 g/dl). Immunological tests including anticardiolipin antibodies were negative. The patient was initially treated (at another centre) with prednisone (1 mg/kg) and monthly intravenous cyclophosphamide (800 mg/m^2), but repeated attempts to lower the prednisone dose below 25 mg/d resulted in acute exacerbations. Parenteral methotrexate 30 mg/week was prescribed. During this treatment he developed right hemiparesis with evidence of cerebral lacunar infarction on the left hemisphere on brain computed tomography, from which he recovered completely. Other corticosteroid sparing agents such as cyclosporine A, oral cyclophosphamide, azathioprine, as well as colchicine, antimalarials and dapsone, failed. In an intent to immunomodulate his severe disease, IVIG (Omr-IgG-am, Omrix) at a dose of 660 mg/kg/day infused over eight hours was administered for three days. A week later the patient developed a diffuse itching urticarial eruption accompanied by an undefined complaint of "weakness in the arms". Three days later, he experienced severe retrosternal pain irradiating to the arms. The electrocardiogram (ECG) showed a 2 mm depression of the ST segment in the inferolateral leads; creatine kinase (CK) increased up to 560 units/ml (normal range < 130, CK-MB: 16%, normal range 4%). Inferolateral acute MI was diagnosed. The patient was treated with aspirin, thrombolytic therapy and heparin for the coronary event; prednisone dose was raised to 40 mg/d. The acute event was complicated by ventricular arrhythmias and 1st degree A-V block from which the patient subsequently recovered. Coronary angiography performed a month later showed diffuse coronary athrerosclerotic changes.

CASE 2

A 41 year old woman, with a family history of coronary heart disease has been suffering for the past four years from biopsy confirmed,

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anti-Jo1 positive polymyositis with progressive interstitial lung disease and considerable muscle weakness. She was treated with prednisone (1 mg/kg) and intravenous pulse cyclophosphamide once a month for three months at another centre. When she gradually improved, immunosuppressive treatment was changed to intramuscular methotrexate 30 mg/week and prednisone was slowly tapered down to 5 mg/d. During this period, she had two events of deep vein thrombosis in both legs and since then was treated with warfarin. Anticardiolipin and circulating anticoagulant were negative. Fifteen months later, she developed fever, bilateral pleural effusions and recurrence of proximal muscle weakness. Prednisone dose was raised to 40 mg/d and IVIG (Omr-IgG-am, Omrix), 1 g/kg/day, infused over eight hours was administered for two days. Immediately after the second pulse of IVIG she first complained of atypical chest pain; ECG was normal. The patient completed 12 months of IVIG treatment with a good response. After the 12th treatment, she reported reccurrent episodes of exertional retrosternal pain; ECG and thalium dipyridamole isotopic heart scan were normal. During this period, the patient developed severe corticosteroid related side effects such as marked obesity, hypertension and diabetes mellitus that required treatment with insulin. Six months later, she exacerbated again with deterioration in her lung function tests and severe muscle weakness. Azathioprine was added and monthly IVIG treatment was renewed. Three days after the third IVIG treatment, she complained of severe retrosternal pain radiating to the neck and arms. An initial ECG was normal but after three days she experienced severe chest pain and fainted. The acute event was complicated by severe bradycardia and a successful resuscitation. ECG disclosed an increase in ST segments in the inferolateral leads. Serum creatine kinase values doubled, with a high MB fraction and troponine levels were found increased. The patient subsequently recovered from this acute event.

CASE 3

A 67 year old man with hypercholesterolaemia and a history of slowly progressive paresthesias, mild distal weakness in both legs and sensory ataxia of three years duration was diagnosed as chronic inflammatory demyelinating polyneuropathy. He did not respond to prednisone treatment (1 mg/kg) given over three months. In view of the severity of his condition and its autoimmune nature, IVIG (Omr-IgG-am, Omrix) was prescribed in a dose of 400 mg/kg/d for five days. A few hours after the first infusion, which lasted three hours, he experienced severe retrosternal pain. An anterior wall non-Q wave MI was confirmed by ECG and increase in creatine kinase values. Cardiac catheterisation performed a month later showed 90% stenosis of the left anterior descending artery, which was widened to 20% stenosis by percutaneous transluminal coronary angioplasty (PTCA). IVIG treatment was renewed at a dose of 0.4 g/kg/d administered over 6–7 hours, under cardiac monitoring, for five days, then once every six weeks. The patient has so far received three additional courses of IVIG without any further complications.

CASE 4

A 67 year old man was diagnosed in 1988 as systemic Castleman disease (plasmacytic variant) whose main manifestations were weight loss, fever, night sweats, lymphadenopathy, Coombs positive haemolytic anaemia and thrombocytopenia. Immunological investigation was negative. The patient was initially treated with prednisone and immunosuppressive drugs including azathioprine, vincristine and cyclophosphamide, with resolution of the systemic symptoms and the lymphadenopathy. However, he still experienced recurrent episodes of severe haemolytic anaemia and thrombocytopenia (with a decrease of his Hb concentrations to 4 g/dl and platelets counts to 20 000/ m^3), which were controlled by immunosuppressive drugs. At the age of 59, he suffered a transient ischaemic attack with right hemiparesis that spontaneously resolved after a few hours. In 1987, he developed Kaposi sarcoma, which was attributed to the immunosuppressive treatment and was therefore stopped. To control the severe immune cytopenias, monthly IVIG (Omr-IgG-am, Omrix) at a dose of 400 mg/kg/d infused over eight hours for five days was given . One day after the completion of the second IVIG course, the patient developed transient right hemiparesis and dysarthria. A left hemisphere stroke was confirmed by brain computed tomography. Despite the possible link between this event and IVIG infusion, in view of the severe haematological picture, IVIG was continued. On day 4 of the fifth course, the patient complained of severe retrostenal pain. Acute inferior wall MI was confirmed by ECG and increased creatine kinase values. The patient subsequently recovered from this acute event.

Discussion

We have presented four patients with resistant autoimmune diseases, who developed acute MI shortly after receiving IVIG treatment: 10 days after the first IVIG infusion in case 1; six days after the 15th infusion in case 2, (although retrospectively, the patient complained previously of retrosternal pain after IVIG treatment); during the first hours after the first infusion in case 3; and on day 4 of the fifth course in case 4. All four patients had some clinical hints and traditional risk factors for pre-existing atherosclerotic vascular diseases. Although the association between MI and IVIG treatment in these patients may be coincidental, the close temporal relation to IVIG treatment suggests that the two events were related.

The first report of thromboembolic complications attributed to IVIG treatment described two patients, aged 62–87 with autoimmune thrombocytopenic purpura (ITP) who developed MI and two patients who had a cerebrovascular accident after IVIG treatment, resulting in death in three of them.[12] Additional sporadic reports have confirmed this association, the

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Table 1 Characteristics of 14 patients with IVIG vascular complications

Patient (ref)	*Age/sex*	*IVIG indication*	*Predisposing factors*	*Other treatments*
A Nine patients with IVIG related MI				
Patient 1[14]	76/F	Uveitis	HC, smoking	CS, AZA, MTX
Patient 2[12]	73/F	ITP	HT, obesity	CS
Patient 3[12]	72/M	RA	HT, obesity	CS
Patient 4[17]	70/M	Thrombopenia	ND	ND
Patient 5[16]	76/M	Neuropathy	HT, MI	ND
Patient 6*	60/M	Polychondritis	HT, CVA	CS
Patient 7*	41/F	Polymyositis	HT, obesity	CS, AZA
Patient 8*	67/M	Neuropathy	HC	CS
Patient 9*	67/M	Cytopenia	TIA	CS
B Six patients with IVIG related thrombotic vascular events other than MI				
Patient 10[13]	84/M	Neuropathy	TIA	none
Patient 11[12]	62/F	ITP	CVA	CS
Patient 12[12]	83/F	ITP	CVA	CS
Patient 13[15]	62/F	ALS	Angina	ND
Patient 14[15]	52/F	Neuropathy	ND	ND
Patient 15[18]	27/F	Myasthenia gravis	Migraine	CS

*Our present cases: HC: hypercholesterolaemia; CS: corticosteroid; AZA: azathioprine; MTX: methotrexate; ITP: immune thrombocytopenic purpura; HT: hypertension; RA: rheumatoid arthritis; ND= not determined; CVA: cerebrovascular accident; TIA: transient ischaemic attack; ALS: amyotrophic lateral sclerosis.

Table 2 Treatment characteristics and outcome in vascular complications following IVIG treatment

Patient (ref)	*IVIG dose*	*Number of treatments*	*Day of the event/event*	*Outcome*
A Patients with MI				
Patient 1[14]	500 g/d,3 days	8	1	Recovery
Patient 2[12]	400 g/d, 5 days	1	3	Death
Patient 3[12]	400 g/d, 5 days	1	6	Death
Patient 4[17]	1 g/d, 2 days	1	1	Death
Patient 5[16]	ND	ND	ND	Death
Patient 6*	650 g/d, 3 days	1	10	Recovery
Patient 7*	1000 g/d, 3 days	15	7	Recovery
Patient 8*	400 g/d, 5 days	1	1	Recovery
Patient 9*	400 g/d, 5 days	5	4	Recovery
B Patients with IVIG related thrombotic events other than MI				
Patient 10[13]	400 g/d, 5 days	1	6 / CVA	Death
Patient 11[12]	400 g/d, 5 days	1	4 / CVA	Death
Patient 12[12]	400 g/d, 5 days	1	5 / CVA	ND
Patient 13[15]	ND	2	2 / PE	Death
Patient 14[15]	400 g/d, 5 days	2	12 / Spinal event	Death
Patient 15[18]	400 g/d, 5 days	1	15 / CVA	Recovery

ND: not determined; CVA: cerebrovascular accident; PE: pulmonary embolism.

main events being cerebrovascular (four cases),[12 13 18] MI (five cases),[12 14 16 17] pulmonary embolism (one case) and acute spinal cord event (one case).[15] Tables 1 and 2 summarise the clinical characteristics of patients who developed MI after IVIG treatment[12–16] for a variety of autoimmune diseases such as ITP, rheumatoid arthritis, uveitis and neurological disorders. Most of them were 60 year old or more (mean age 66, range 41–76) and all but one had a previous history of atherosclerosis or risk factors, such as hypertension, stroke, previous MI, hyperlipidaemia and obesity. It thus seems that MI or other acute ischaemic events after IVIG tend to occur in patients with pre-existing atherosclerotic disease. Our present cases support this hypothesis while the follow up of case 3 reconfirms this view from another direction: after the coronary stenosis was corrected by percutaneous translunial coronary angioplasty, the patient received additional infusions of IVIG without further complications.

The frequency of thromboembolic events attributable to IVIG is estimated to be between 3% and 5%.[19 20] In one of the medical centres who participated in this study (Tel Aviv Medical Centre), our own experience includes 40 patients treated with IVIG during the past 10 years, two of them developed MI. These numbers are similar to the rate of thromboembolic phenomena reported by Haplea *et al*. These authors have investigated the association between IVIG and thromboembolic events in 295 patients and found a total of 16 events—five cerebrovascular or transient ischaemic events, one MI, nine pulmonary embolism/deep vein thrombosis and one arterial embolism. Nine cases occurred within 24 hours from the infusion, while seven occurred more than 24 hours and less than 30 days after the infusion.[20] Similar conclusions may be drawn from reviewing other documented case reports (table 2): the event occurred after the first infusion in five patients, in four of them on the day they received IVIG or a few days later in the others.

The outcome of these events was generally poor resulting in death in four of nine MI patients, and in four of six patients with cerebral events.

Infusion of IVIG may affect the cardiovascular system by two different mechanisms, which may operate synergistically: it may induce expansion of plasma volume with consecutive hypertensive reactions, increased oxygen demand and cardiac decompensation on the one hand,[19] and increase in plasma and blood viscosity on the other hand.[15 17] Reinhart *et al* have shown that plasma viscosity increased to beyond the normal range after IVIG treatment and that the concentration of infused IgG correlated strongly with the viscosity of plasma and whole blood, both in vivo and in vitro.[17] Dalakas has reported an increment in viscosity after IVIG from 0.1 to 1 centipoise in 13 patients, the increase being higher in patients with paraproteinaemic polyneuropathy[15] and recommended monitoring of serum viscosity in elderly patients and in those with paraproteinaemias, high lipoproteins values or pre-existing vascular diseases.[15] Blood viscosity is an important determinant of subendocardial oxygen delivery.[21] Increased blood viscosity may induce myocardial ischaemia through rouleaux formation, cross linking of fibrin and thrombosis.[22] As blood viscosity may be already increased in people with stable angina pectoris,[23] any further increment may result in overt ischaemia and MI.

In conclusion, we presented four patients who developed acute MI shortly after IVIG infusion. All four patients had pre-existing risk factors for coronary heart disease and atherosclerosis. As the number of IVIG treated patients in each individual centre is relatively small, and the incidence of these complications is relatively low, awareness to cumulative data on this rare but potentially fatal adverse event is of particular importance. It may dictate a more prudent attitude toward a treatment that has been considered relatively safe apart from its high cost. In patients with vascular risk factors such as old age, hypertension, hyperviscosity states, history of stroke or coronary artery disease, IVIG should be prescribed with a cautious reweighted risk/benefit consideration.

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