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Use of Intravenous Immunoglobulin Therapy at Unconventional Doses in Refractory Fulminant Systemic Lupus Erythematosus

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ABSTRACT

The use of human intravenous immunoglobulins (IVIg) in systemic lupus erythematosus (SLE) currently relies on evidence from small case series and is mainly regarded as an off-label strategy in cases that are refractory to conventional therapies or poorly controlled with high doses of corticosteroids. Standard dosage regimens typically entail the administration of a total amount of 2 g/kg of IVIg divided into five consecutive days in order to minimize the risk of severe adverse events. We herein describe the case of a 28-year-old woman with a known history of antiphospholipid syndrome (APS) who was admitted to our hospital following fulminant onset of SLE in spite of ongoing immunosuppressive therapy. Acute renal insufficiency with nephrotic-range proteinuria, central nervous system involvement, severe thrombocytopenia, malar rash, pancreatic injury and moderate-severe aortic valve steno-insufficiency were the most prominent clinical manifestations, along with high titres of anti-dsDNA antibodies. Pulses of methyl-prednisolone followed by high-dose corticosteroids proved ineffective. Strikingly, IVIg therapy delivered at unconventional doses (1.2 g/kg) due to the presence of multiple risk factors for adverse events resulted in a significant, comprehensive clinical improvement. Although large-scale randomized double-blind studies are needed, the use of IVIg might constitute a valuable therapeutic modality as a last-resort strategy in cases of fulminant SLE. The total dose of immunoglobulins should be dictated by the clinical response as well as the presence of pre-existing risk factors for adverse events.

LEARNING POINTS

- The use of immunoglobulins in the treatment of systemic lupus erythematosus is mainly based on small prospective studies and case series.
- Their use as a rescue strategy in cases of systemic lupus erythematosus that are refractory to conventional immunosuppressive therapy may be a valid therapeutic alternative in selected patients.
- The short-term clinical response and the presence of risk factors for adverse effects should dictate the overall dose of immunoglobulins administered to the patient.

KEYWORDS

Intravenous human immunoglobulins; refractory fulminant systemic lupus erythematosus

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CASE DESCRIPTION

A 28-year-old woman with a known history of antiphospholipid syndrome (APS) and chronic kidney disease with proteinuria was admitted to our hospital because of fever and acute abdominal pain.

Seven days before admission, the patient was seen by her primary care physician due to the onset of fever, chills and general malaise and was administered empirical antibiotic therapy. Five days after initiation of therapy, she was still febrile and had progressive abdominal pain. Pain was referred to as excruciating, persistent, and mainly localized at the epigastrium and the lower abdominal quadrants, as well as invariably worsened by meals.

The patient had a history of primary APS, which had started 10 years earlier as catastrophic APS with multi-organ failure secondary to microangiopathic haemolytic anaemia, severe thrombocytopenia and aortic valve involvement. Evidence of kidney damage with mild proteinuria was initially found 3 years earlier and a slightly elevated titre of anti-ds-DNA autoantibodies was detected for the first time 2 years before the current presentation. A diagnosis of lupus-like syndrome was then established. Medications included aspirin 100 mg once daily, prednisone 5 mg once daily, mycophenolate mofetil 1 g twice daily, valsartan 20 mg once daily, furosemide 25 mg once every 48 hours, spironolactone 25 mg once every 48 hours, and pantoprazole 20 mg once daily. The patient had no known drug allergies. In the past, azathioprine withdrawal was required due to epigastric pain.

In the emergency department, the patient appeared ill. Her temperature was 38.0°C, blood pressure 145/100 mmHg, heart rate 108 beats per minute and peripheral oxygen saturation 99% in ambient air. On examination, livedo reticularis was widespread throughout the body. The abdomen was extremely tender at the epigastrium as well as the lower abdominal quadrants. Blumberg, Murphy and Giordano manoeuvres were negative. On auscultation, a low-intensity, low-pitched, decrescendo, blowing diastolic murmur was detected at the mesocardium and second right intercostal space. Signs of mild congestion were present. The remainder of the examination was normal. As shown in *Table 1*, laboratory data demonstrated further worsening of renal function, significant thrombocytopenia, mild elevation of lactate dehydrogenase, and high levels of C-reactive protein.

Parameter	*Reference range*	*6 Months before*	*On admission*	*3 Hours before IVIg*	*5 Days after first IVIg dose*	*30 Days after IVIg infusion*
BUN (mg/dl)	*<23*	*34*	*27*	*57*	*49*	*47*
Creatinine (mg/dl)	*0.5–1.2*	*1.22*	*1.89*	*2.30*	*1.86*	*1.85*
Albumin (g/dl)	*3.5–5.0*	*4.3*	*3.0*	*3.5*	*3.1*	*–*
Proteins (g/dl)	*6.5–8.5*	*7.7*	*6.8*	*5.6*	*6.1*	*–*
Amylase (IU/l)	*<100*	*–*	*92*	*414*	*321*	*154*
Lipase (IU/l)	*6.5–8.5*	*7.7*	*6.8*	*5.6*	*6.1*	*–*
LDH (IU/l)	*<250*	*203*	*288*	*383*	*240*	*204*
ESR (sec)	*<30*	*–*	*120*	*2*	*20*	*–*
Platelets (×10⁹/l)	*0–5.0*	*–*	*196*	*6.57*	*2.43*	*–*

Table 1. Chemistry panel
BUN: blood urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

Upon admission to the Division of Internal Medicine, nephrotic-range proteinuria was detected, and trans-thoracic echocardiography showed moderate-severe aortic insufficiency and moderate aortic stenosis with no endocardial vegetations. On day 2, an episode of generalized tonic-clonic seizures occurred, which warranted initiation of therapy with i.v. diazepam and 24-hour monitoring in the intensive care unit. As a second bout of catastrophic APS was highly suspected, the patient underwent five cycles of plasma exchange, but this was followed by no evidence of clinical improvement. High titres of ANA and anti-dsDNA autoantibodies were subsequently detected, while titres of antiphospholipid antibodies were broadly similar to those seen 6 months earlier (*Table 2*). A direct Coombs test was positive, although no laboratory evidence of microangiopathic haemolysis was found. Complement C3 and C4 levels were markedly reduced. A comprehensive

diagnosis of SLE with fulminant multi-systemic involvement was finally made. Due to the high risk of haemorrhage and the severity of the disease, kidney biopsy was delayed. Methyl-prednisolone pulses were administered over three consecutive days, followed by prednisolone 1 mg/kg/day. The remainder of the therapy included mycophenolate 1 g twice daily, levetiracetam 500 mg twice daily, valsartan 80 mg twice daily, a basal-bolus insulin regimen and weekly darbepoetin-alpha injections.

Despite high-dose immunosuppressive therapy, no sign of clinical improvement was seen 12 days after admission.

Severe epigastric pain persisted and amylase and lipase levels were progressively rising. A malar rash developed, and platelet count declined to 14,000/mm^3 (*Table 2*).

Variable	Reference range	6 Months before admission	On admission	5 Days after first IVIg dose	30 Days after IVIg infusion
ANA	Negative	1:160 Homogeneous pattern	1:1280 Homogeneous pattern	-	1:640 Homogeneous pattern
Anti-dsDNA (AU/ml)	<50	86.6	312.4	62.4	48.8
Anti-ENA (AU/ml)	<10	–	Negative	–	–
Beta2-GP1 IgG (U/ml)	<20	254.5	138.7	35.8	35.5
Beta2-GP1 IgM (U/ml)	<10	5.0	5.7	2.0	1.6
Anticardiolipin IgG (MPLV/ml)	<20	152.9	90.1	15.4	13.0
Anticardiolipin IgM (MPLV/ml)	<10	–	2.4	0	0.2
LAC	Negative	+++	+++	–	+++
C3 (mg/dl)	90–180	–	55	54	61
C4 (mg/dl)	10–40	–	2	5	6

Table 2. Autoimmunity panel

ANA: antinuclear antibodies; anti-dsDNA: anti–double-stranded-DNA antibodies; anti-ENA: anti-extractable nuclear antigen antibodies; beta2-GP1: beta2-glycoproetin 1; LAC: lupus anticoagulant.

Serum creatinine further increased, higher levels of proteinuria were detected (3.8 g/24 hours), and IgG levels were abnormally low (466 mg/dl). Mental function was also fluctuating, with evidence of poor capacity to focus, remarkable daytime drowsiness and decreased psychomotor activity.

Following a multidisciplinary discussion, with the prior informed consent of the patient, combination therapy with intravenous human polyclonal immunoglobulins followed by administration of rituximab was undertaken. The patient was given a total of 1.2 g/kg of IVIg devoid of sucrose in divided doses over three consecutive days (days 13, 14, 15) using a slow-infusion protocol. Since the patient had pre-existing renal insufficiency and a very high risk of thromboembolic events and congestive heart failure, higher doses of immunoglobulins were not administered. No immediate or late adverse reactions occurred.

A significant clinical improvement was observed 72 hours after the first infusion. Abdominal pain reduced, and the butterfly rash disappeared. Kidney function improved and 24-hour proteinuria dropped from 2 g/l to 0.5 g/l. Platelet count and C3 and C4 levels progressively increased. Titres of anti-dsDNA autoantibodies had fallen to near-borderline levels (62.4 IU/l) 5 days after the first Ig infusion. Signs of central nervous system involvement gradually resolved.

On day 18, rituximab was administered intravenously at a dose of 375 mg/m^2 and then delivered once a week for three more weeks, without complications. Two months after her first admission to hospital, the patient appeared to be well and free of symptoms. Anti-dsDNA autoantibodies are currently below the borderline level. Current immunosuppressive therapy includes prednisone according to a tapering schedule and mycophenolate mofetil 1 g twice daily. In addition, the patient is undergoing a monthly infusion of immunoglobulins due to their proven potential long-term efficacy in patients with SLE[3].

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DISCUSSION

At present, the use of human intravenous immunoglobulins (IVIg) in SLE is reserved for severe and/or refractory cases as well as when the disease is only controlled with high-dose corticosteroids[1, 2]. The clinical efficacy and indications for IVIg need further investigation due to the current lack of large-scale double-blind randomized clinical trials. However, a number of case series have been reported with encouraging results, although evidence is limited by the heterogeneity of protocols applied and the variability of clinical manifestations successfully treated[4–6]. In addition, in our patient with worsening renal function and a permanent state of hypercoagulability, several concerns were raised about the potential adverse effects of IVIg. Furthermore, due to significant aortic insufficiency and overt nephrotic syndrome, adequate hydration before and during immunoglobulin infusion was performed, and fluid balance and urine output were carefully monitored.

However, the fulminant onset of the disease as well as the multisystem involvement warranted prompt therapeutic intervention, and salvage therapy with a rapid onset of action was needed. Therefore, on the basis of the currently available evidence, human polyclonal IVIg were administered.

The protocol most often used in clinical practice entails high-dose IVIg infusion, consisting of a total amount of 2 g/kg body weight, usually divided into five daily doses of 400 mg/kg each to minimize the risk of adverse events[1]. However, dosage regimens have not been fully explored and are still a matter of debate among experts. In order to prevent high-risk severe adverse events, including thromboembolism and worsening renal insufficiency, we opted for a lower dose of IVIg (400 mg/kg/day for three consecutive days), which has not been previously reported in the literature to our knowledge. Remarkably, an unprecedented clinical response was noted 72 hours after the first dose, and included every affected organ and system, along with concurrent progressive normalization of the major immunological parameters. Clinical response was still consistent after 2 months following four administrations of rituximab at a dose of 375 mg/m2. The SLEDAI score dropped from 33 to 3, indicating near-to-complete remission of the disease.

This case demonstrates that immunoglobulins can constitute a valuable therapeutic modality as a last-resort strategy in cases of fulminant SLE. Because there is scant evidence concerning the use of low-intermediate doses, the total amount of immunoglobulins delivered to the patient should be dictated by the clinical response in the short term and the presence of risk factors for adverse events. Regardless of their long-term efficacy, these positive results should encourage thoughtful use of IVIg in all cases refractory to conventional therapies or uncontrolled with high doses of corticosteroids.

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