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Immunomodulation for treatment of drug and device refractory gastroparesis

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ABSTRACT

Objective: Patients with generalized autoimmune dysautonomia may also present with gastroparesis. Immune dysfunction in such patients can be evaluated using antibodies to glutamic acid decarboxylase (GAD) and full thickness biopsy of stomach. In this study, we utilize immunotherapy for treatment of drug and Gastric Electrical Stimulation (GES) resistant gastroparetic patients with evidence of neuroinflammation on full thickness gastric biopsy and had positive GAD65 autoantibodies.

Material and methods: We conducted a retrospective chart review of 11 female patients with drug and device resistant gastroparesis. Patients were treated for a total of 8–12 weeks with either intravenous immunoglobulin (IVIg), or combined mycophenolate mofetil (MM) and methylprednisolone, or only MM. Patients were excluded if they had previous side effects from steroid therapy, low scores on dual-energy X-ray absorptiometry (DEXA) scan results, immune-compromised conditions with infections like tuberculosis and zoster. Symptoms of nausea, vomiting, abdominal pain, early satiety/anorexia, bloating and total symptom score (TSS) as reported by the patients were recorded before and after the treatment at a follow up visit 2 to 16 weeks after initiation of therapy.

Results: Maximum symptom improvement was seen in patients treated with IVIg (67%). 6 patients (55%) had improvement in vomiting, whereas 5 patients (45%) had improvements in nausea, abdominal pain and bloating.

Conclusions: Immunomodulatory therapy shows positive outcomes in improving vomiting symptom in some gastroparetic patients who have coexisting positive autoimmune profiles. This preliminary data suggests the need for further investigations in immunotherapy targeted to patients with gastroparetic symptoms refractory to approved drug and device therapies.

1. Introduction

Gastrointestinal motility disorders can be found in the setting of generalized autoimmune dysautonomia and may present as gastroparesis [1]. Several antibodies have been associated with autoimmune disorders presenting with symptoms of gastroparesis [2]. Antibodies to Glutamic Acid Decarboxylase (GAD) have been described in Type 1 diabetes mellitus, and anti-GAD65 is the most studied isoform [3,4]. Antibodies to GAD have also been extensively studied in many other autoimmune disorders like Stiff-Person Syndrome (SPS) and Dermatomyositis [5,6]. High titers of GAD antibodies signify autoimmune dysfunction and the use of immunomodulating drugs may be indicated for symptomatic patients with these markers. Studies have shown the benefits of immunomodulatory therapy in such conditions; however, it has been systematically applied only in SPS [5].

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Immune dysfunction in gastroparesis is also evident on full thickness biopsy of the stomach. Patients with gastroparesis show increased CD45 immunofluorescence in the myenteric plexus and increased CD68 infiltration in the muscle layers, significant of increased immune cells and macrophages expression, respectively, in the stomach [7]. Along with evidence of immune dysfunction, gastroparetic patients also have decreased number of interstitial cells of Cajal and decreased nerve fibers [7].

Immunotherapy has been utilized for patients with autonomic neurological disorders. Using the same concept, immunotherapy trial has been utilized with good results for evaluation of patients with presumed autoimmune gastrointestinal dysmotility [8]. In this study, we utilize immunotherapy for treatment of drug and GES resistant patients with symptoms of gastroparesis who were positive for gastric enteral neuroinflammation on full thickness gastric biopsy and had positive GAD65 autoantibodies.

2. Methods

2.1. Study design

This is a retrospective case series of patients identified through medical chart review. The clinical protocol was reviewed and approved by the University of Louisville Institutional Review Board.

2.2. Study subjects

We included gastroparetic patients who had sub-optimal response to medical therapy and/or gastric enteral stimulation therapy. All patients had evidence of neuroinflammation as defined by positive GAD65 antibodies and presence of inflammatory markers on full thickness gastric biopsy. Western blotting (ANABLOT) was used to identify human auto-antibodies present in serum with specificity for a number of antibodies including Scl 70, Scl 105, SSB 43, Sm 16, Sm 18, and Ku 66. A scaled GI banding score or GIBS was used to standardize the bands present. All patients also had evaluation of paraneoplastic antibody panel which included antineuronal nuclear autoantibody type 1, 2, and 3 (ANNA-1, ANNA-2, ANNA-3), anti-glial nuclear antibody (AGNA), Purkinje Cell Cytoplasmic Antibody Type-1 (PCA-1), Purkinje Cell Cytoplasmic Antibody Type-2(PCA-2), Purkinje Cell Cytoplasmic Antibody Type Tr (PCA-Tr), Amphiphysin Antibody, CRMP-5 antibody, Striated Muscle antibody, P/Q-Type Calcium Channel Antibody, N-Type Calcium Channel Antibody, ACh Receptor (Muscle) Binding Antibody, AChR Ganglionic Neuronal Antibody, Neuronal (V-G) K+ Channel Antibody. Patient exclusion criteria included: previous side effects from steroid therapy, low scores on dual-energy X-ray absorptiometry (DEXA) bone scan results, immune-compromised conditions with infections such as tuberculosis and zoster.

3. Methods

All patients in the study received therapy with immunosuppressive therapy with either intravenous immunoglobulin, or mycophenolate mofetil (MMF), or combined daily mycophenolate mofetil according to the protocol at our center. Intravenous immunoglobulin or IVIg (this medication is available by a number of trade names: Carimune NF-BDI Pharma, Columbia, SC; Flebogamma 5% DIF-Grifols, Los Angeles, CA; Gamunex 10%-Talecris, Durham, NC; Gammagard S/D-Baxter, Deerfield, IL; Octagam 5%-Octapharma, Toronto, ON) was given weekly for 8–12 weeks. Mycophenolate Mofetil or MMF (CellCept, Genentech, South San Francisco, California) was given daily for 12 weeks. Combined MMF and intravenous or oral methylprednisolone (Medrol, Pfizer, New York, New York) were given daily for 8–12 weeks. Symptoms of nausea, vomiting, abdominal pain, early satiety/anorexia, and bloating as reported by the patients on a 5 point scale of 0–4 with 4 being the worst, were recorded before and after the treatment. Total symptom score (TSS) was calculated by addition of all the symptom scores. All patients were continued on their medications for symptomatic management of gastroparesis and had their GES turned ON. Patients were followed up at clinical visit or by phone call from 2 to 16 weeks after the initiation of therapy to monitor the response with final determination of therapeutic response performed after at least 12 weeks of therapy.

4. Results

Our clinical series included 11 female gastroparesis patients (10 Caucasians, 1 African-American) with mean of age 45 years. Ten patients had a history of idiopathic gastroparesis and 1 patient had diabetic gastroparesis. Three patients were treated with IVIg, four with combined methylprednisolone and mycophenolate mofetil, and four with mycophenolate mofetil only (Table 1). ANABLOT performed on 8 patients showed 7 patients with more than 3 bands each giving them GIBS ≥ 3 (normal < 3). Paraneoplastic antibodies were found in 2 patients. Symptom scores were recorded in all the 11 patients (Table 2). Among the patients who

Table 1
Baseline antibody profiles of gastroparesis patients selected for immunotherapy treatment.

Patient no.	Immunotherapy treatment	ANABLOT (no. of bands)	Paraneoplastic Antibodies	GAD65
1	Mycophenolate mofetil	5	Negative	Positive
2	Mycophenolate mofetil and Methylprednisolone	5	Negative	Positive
3	Mycophenolate mofetil and Methylprednisolone	4	Negative	Positive
4	Mycophenolate mofetil	7	Negative	Positive
5	Mycophenolate mofetil	2	0.03	Positive
6	Mycophenolate mofetil and Methylprednisolone	6	Negative	Positive
7	Mycophenolate mofetil and Methylprednisolone	JO-1–0.6	Negative	Positive
8	Mycophenolate mofetil	7	Negative	Positive
9	Immunoglobulin	JO-1–0.3	Negative	Positive
10	Immunoglobulin	JO-1–1	0.03	Positive
11	Immunoglobulin	4	Negative	Positive

GAD65: antibodies to glutamic acid decarboxylase, isoform 65.
JO-1: antibodies to cytoplasmic protein, histidyl tRNA.
ANABLOT: western blot for human auto-antibodies including Scl 70, Scl 105, SSB 43, Sm 16, Sm 18, and Ku 66.
Paraneoplastic antibodies: ANNA-1, ANNA-2, ANNA-3, AGNA, PCA-1, PCA-2, PCA-Tr, Amphiphysin Antibody, CRMP-5 antibody, Striated Muscle antibody, P/Q-Type Calcium Channel Antibody, N-Type Calcium Channel Antibody, ACh Receptor (Muscle) Binding Antibody, AChR Ganglionic Neuronal Antibody, Neuronal (V-G) K+ Channel Antibody.