

Novel Approaches to Treatment of Immune-Mediated Chronic Intestinal Pseudo-Obstruction

Andreu Vilaseca,^{1,2} Paula Arranz,³ Arnau Llauro, ^{2,3} Ana Zabalza,^{1,2} Elianet Gisell Fonseca,^{4,5} Inmaculada Medina,⁶ Maria Amelia Gómez Lorente,⁶ Luis Alcalá-González,^{2,7} Natalia Borrue, ^{2,7} José Luis Fernández-Forcelledo,⁸ Helena Ariño,^{1,2} Thais Armangue,^{4,5} Xavier Montalban,^{1,2,9} Francesc Graus,^{4,*} and Carolina Malagelada^{2,7,*}

Correspondence

Dr. Vilaseca
avilaseca@cem-cat.org

Neurol Neuroimmunol Neuroinflamm 2025;12:e200369. doi:10.1212/NXI.0000000000200369

Abstract

Background and Objectives

The optimal immunosuppressive treatment for autoimmune chronic intestinal pseudo-obstruction (CIPO) is unknown due to lack of clinical trials. Even less data exist on treatment recommendations for patients who do not respond to first-line immunotherapy.

Methods

We describe 4 patients with autoimmune CIPO treated with vedolizumab (3/4), a monoclonal antibody that interferes the lymphocyte trafficking to the gastrointestinal tract, or rituximab (1/4) who did not respond to steroids or IV immunoglobulins. We made a systematic review of previously published cases of CIPO treated with these biological agents.

Results

Vedolizumab was effective in 2 of 3 patients but failed in a child with nonparaneoplastic anti-Hu-associated CIPO, who had generalized dysautonomia. The 2 patients who responded to vedolizumab had an isolated CIPO, and they did not present neuronal antibodies. Rituximab was prescribed in a case of anti-Hu-associated, nonparaneoplastic CIPO, who showed a complete clinical response after this treatment. Our review of the literature retrieved 4 previous cases of autoimmune CIPO treated with rituximab but none treated with vedolizumab. All patients treated with rituximab had Hu antibodies. Two patients showed a clinical response to the treatment with rituximab.

Discussion

Our findings underscore the potential efficacy of rituximab and vedolizumab in the management of autoimmune CIPO refractory to first-line treatments.

Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare syndrome characterized by severe intestinal dysmotility in the absence of a mechanical obstruction.¹ Among the various etiologies of CIPO, immune-mediated mechanisms stand out as a significant cause.^{2,3} CIPO autoimmunity specifically targets neurons in the myenteric plexus, either in isolation or as part of a generalized autoimmune autonomic ganglionopathy which associates with ganglionic acetylcholine receptor in approximately 50% of the patients.⁴ CIPO may also be a paraneoplastic syndrome associated with Hu antibodies and small cell lung cancer (SCLC) or neuroblastoma.

*These authors contributed equally to this work as co-senior authors.

¹Neurology Department and Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari de Vall d'Hebron, Barcelona, Spain; ²Universitat Autònoma de Barcelona (UAB), Spain; ³Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain; ⁴Neuroimmunology Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) Institut d'Investigacions Biomèdiques August Pi i Sunyer; ⁵Pediatric Neuroimmunology Unit, Neurology Department, Sant Joan de Déu Children's Hospital, Barcelona, Spain; ⁶Pediatric Section, Hospital Virgen de las Nieves, Granada, Spain; ⁷Gastroenterology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Barcelona, Spain; ⁸Gastroenterology Department, Hospital Sierrallana, Torrelavega, Spain; and ⁹Universitat de Vic-Universitat Central de Catalunya (UVic-UCC), Spain.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

In this setting, CIPO may occur isolated or with a concomitant sensory neuropathy or CNS involvement.² Autoimmune CIPO has also been described in a few patients with myasthenia gravis and thymoma.⁵

Evaluation of the optimal treatment for autoimmune CIPO is difficult due to the lack of prospective clinical trials. There are even less data to decide which treatment should be recommended in patients who do not respond to first-line immunotherapy (steroids, IV immunoglobulins, and plasmapheresis). In several autoimmune neurologic disorders, rituximab is the second-line drug of choice and other biological agents (inebilizumab, natalizumab, daratumumab, and tocilizumab) are being explored.⁶

In this study, we describe 4 patients with autoimmune CIPO who received the monoclonal antibodies rituximab, targeting the B-cell surface CD20 antigen, or vedolizumab, that binds to the lymphocyte $\alpha 4\beta 7$ integrin interfering with the lymphocyte trafficking specifically to the gastrointestinal tract, and we review the published evidence of cases of CIPO treated with these drugs.

Methods

Patients provided informed consent and shared their perspectives. We searched MEDLINE and Embase for articles published in English before May 1, 2024, using the MeSH terms “enteric neuropathy,” “Intestinal Pseudo-obstruction,” “Gastroparesis,” “Dysmotility,” and “Rituximab,” or “Vedolizumab.” Cases with adequate clinical information were included in the review.

Data Availability

Anonymized data are available by request.

Results

Patient 1

A 45-year-old man presented with abdominal discomfort. His medical history included diagnosis of ocular myasthenia gravis 3 years before, which required thymectomy to neurologically improve. One year after surgery, the patient developed dysphagia. Esophageal manometry detected type I achalasia. Treatment with pyridostigmine and prednisone was ineffective, and he required endoscopic dilatation for symptomatic relief. Four years later, he presented with vomiting, constipation, and acute abdominal pain. Abdominal tomography showed severe small bowel dilatation. Serologic studies were negative for neuronal antibodies. A small bowel biopsy demonstrated myenteric plexus inflammation (myenteric ganglionitis) with a predominance of CD8+ T cells and scarce B cells, with a reduction of ganglionic neurons (Figure 1). After partial improvement with oral prednisone and no improvement with azathioprine, vedolizumab was initiated, leading to both clinical and

radiologic improvement (Figure 2). Corticosteroid therapy was tapered to a maintenance dose of 10 mg/day, in combination with vedolizumab (300 mg each 4 weeks), with no relapse of the gastrointestinal symptoms after 12 months of follow-up.

Patient 2

A 7-year-old North-African boy presented with a history of subacute sensory neuropathy. A comprehensive workup was negative except for the presence of serum Hu antibodies. Extensive screening for an associated tumor was negative. Monthly cycles of IVIg resulted in the stabilization of symptoms. Three years later, the patient experienced recurrent episodes of incoercible vomiting, abdominal distention, and hypertensive crises. Abdominal x-rays performed during the acute episodes showed dilated intestinal loops with air-fluid levels. In addition, bilateral Adie’s pupils were noted on neurologic examination. Serum Hu antibodies were positive confirming an autoimmune CIPO with generalized autonomic dysfunction. Subsequent neoplasm screening yielded negative results. Vedolizumab was added to his regular IVIg maintenance therapy. However, gastrointestinal symptoms did not improve.

Patient 3

A 19-year-old woman presented with a history of repetitive postprandial vomiting, abdominal distension, and constipation. Having lost 15 kg 6 months after onset, she was placed on parenteral nutrition. Abdominal CT demonstrated severe colonic and small bowel dilatation. Serologic studies revealed Hu antibodies. Repeated studies to detect a tumor were always negative. A small bowel biopsy revealed a diminished number of neuron cells in the myenteric plexus with inflammatory infiltrates characterized by a predominance of CD8+ T cells. Treatment with prednisone and adalimumab was not effective. Treatment was changed to IV methylprednisolone, IVIg, and rituximab with marked clinical improvement which has persisted for 12 months, with only mild symptoms under continued treatment with rituximab and prokinetics.

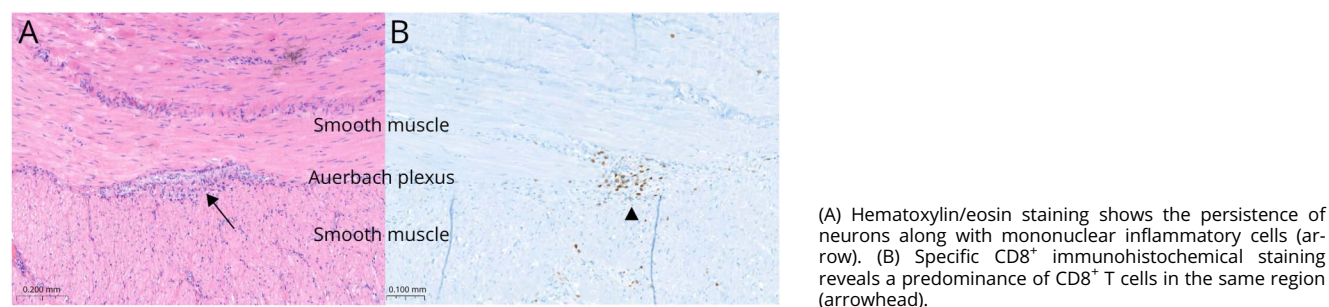
Patient 4

A 66-year-old woman, presented over the previous 6 years repetitive episodes of nonmechanical intestinal occlusion and severe malnutrition, requiring chronic parenteral nutrition. Neuronal antibodies including ganglionic acetylcholine receptor and Hu were negative. A small bowel biopsy revealed myenteric ganglionitis. The patient started treatment with prednisone with initial response, but relapsed. Then, vedolizumab was started, and the patient presented a significant clinical improvement, allowing oral intake, normalization of body weight, and cessation of parenteral support, persisting remission after 12 months.

Systematic Review of Previously Reported Patients Treated With Rituximab and Vedolizumab

Our review identified 4 previous case reports of CIPO treated with rituximab (2 in combination with cyclophosphamide),

Figure 1 Histologic Examination of the Intestinal Biopsy



but none treated with vedolizumab. All treated patients had Hu antibodies. Among these, 2 cases were paraneoplastic, associated with neuroblastoma and SCLC, respectively. Two patients showed a favorable clinical response to the treatment with rituximab (Table).

Discussion

Our small case series provides some insights on the potential beneficial effect of vedolizumab and rituximab in the treatment of autoimmune CIPO resistant to first-line immunotherapies. Despite the absence of previous evidence, we used vedolizumab because of its selective effect on the gastrointestinal tract and the similarity with natalizumab.⁷ Like vedolizumab, natalizumab prevents the entrance of lymphocytes to brain by blocking the interaction of the lymphocyte $\alpha 4$ -integrin subunit with its ligands in endothelial cells,⁸ and it has shown efficacy in a few patients with anti-Hu paraneoplastic CNS syndromes.⁷ Vedolizumab was effective in the 2 patients with isolated CIPO, but it failed in the child with nonparaneoplastic anti-Hu-associated CIPO, who had a generalized dysautonomia involving both the sympathetic and parasympathetic nervous systems.

One of the patients who responded to vedolizumab had an associated myasthenia and thymoma. This association has

been previously documented in around 25 patients. A few of them present onconeural (mostly Hu or CRMP5) or ganglionic acetylcholine receptor antibodies,⁹ and in general, these patients often show a clinical response to immunotherapy.¹⁰

In contrast to thymoma-associated CIPO, cases associated with Hu antibodies are less responsive to immunosuppressive treatment. Whereas one of our patients with Hu antibodies (patient 2) did not improve with vedolizumab, another responded to treatment with rituximab (patient 3). Clinical response was also observed in 2 of 4 cases reported in the literature. Taking together our data and the previously reported cases, there is evidence that rituximab may be an effective therapeutic option for anti-Hu-associated CIPO, more likely in nonparaneoplastic cases. The presence of a neoplasm seems to be a predictor for a poorer response to immunosuppressive therapy in anti-Hu gastrointestinal dysmotility.¹¹ A retrospective review in anti-Hu patients suggested that nonparaneoplastic cases were more likely to respond (6.7% compared with 37.5% in those with an associated tumor). The predominant T-cell infiltrates in intestinal biopsies and the loss of myenteric neurons suggest a pathophysiology similar to other paraneoplastic neurologic disorders.⁶ Rituximab's effectiveness may seem counterintuitive given the role of CD8+ T cells in pathophysiology¹¹; however,

Figure 2 Radiologic Response After Treatment



Table Patients With CIPO Treated With Rituximab or Vedolizumab

First author (ref)	Age/sex	Additional neurological symptoms	Antibody	Intestinal pathologic examination	Cancer	Failed immunotherapies	Second-line drug and response
Coret ¹²	60/F	Sensory neuronopathy	Hu	Not done	None	Corticosteroids, IVIG, PLEX	Rituximab. CIPO: complete response; sensory neuronopathy: partial response
Badari ¹³	61/M	No	Hu	Diffuse lymphoplasmacytic infiltration of myenteric plexus	SCLC	IVIG, octreotide	Rituximab. Complete response (concomitant treatment with cyclophosphamide)
Drukker ¹⁴	4/M	Sensory neuropathy	Hu	Lack of ganglion cells in myenteric plexus	Neuroblastoma	Prednisone	Rituximab. No response ^a
Schamphelaere ¹⁵	58/M	Brainstem and limbic encephalitis	Hu	T-cell infiltration of myenteric plexus	None	Prednisone and PLEX	Rituximab. No response (concomitant treatment with cyclophosphamide)
Vilaseca (patient 1)	45/M	Myasthenia gravis	None	CD8+ T cells myenteric ganglionitis, reduction of ganglionic neurons	Thymoma	Prednisone and azathioprine	Vedolizumab and low-dose prednisone. Clinical and radiologic response after 12 mo of follow-up
Vilaseca (patient 2)	7/M	Sensory neuropathy and dysautonomia	Hu	—	None	IVIg	Vedolizumab. No response
Vilaseca (patient 3)	19/F	No	Hu	CD8+ T cells myenteric ganglionitis, reduction of ganglionic neurons	None	Prednisone, adalimumab	Methylprednisolone, IVIg, rituximab. Clinical and radiologic response after 12 mo of follow-up
Vilaseca (patient 4)	66/F	No	None	T-cell infiltration myenteric ganglionitis	None	Prednisone	Vedolizumab. Clinical and radiologic response after 12 mo of follow-up

Abbreviations: CIPO = Chronic Intestinal Pseudo-obstruction; IVIg = IV immunoglobulins; PLEX = plasma exchange; SCLC = small cell lung cancer.

^a PLEX induced a CIPO remission that was initially maintained by rituximab. Despite this treatment there were 4 relapses over the ensuing 17 months.

CD20⁺ T cells and B cells capable of antigen presentation may contribute to this response.⁶ This finding also suggests the importance of a narrow temporal window to prevent permanent neurologic dysfunction in patients with CIPO.

In conclusion, our findings indicate that rituximab and vedolizumab should be considered in the management of autoimmune CIPO refractory to first-line treatments.

Author Contributions

A. Vilaseca: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. P. Arranz: drafting/revision of the manuscript for content, including medical writing for content. A. Llauro: drafting/revision of the manuscript for content, including medical writing for content. A. Zabalza: drafting/revision of the manuscript for content, including medical writing for content. E. Gisell Fonseca: drafting/revision of the manuscript for content, including medical writing for content. I. Medina: drafting/revision of the manuscript for content, including medical writing for content. M.A. Gómez Lorente:

drafting/revision of the manuscript for content, including medical writing for content. L. Alcalá-González: drafting/revision of the manuscript for content, including medical writing for content. N. Borruel: drafting/revision of the manuscript for content, including medical writing for content. J.L. Fernández-Forcelledo: major role in the acquisition of data. H. Ariño: drafting/revision of the manuscript for content, including medical writing for content. T. Armangue: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. X. Montalban: drafting/revision of the manuscript for content, including medical writing for content. F. Graus: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Malagelada: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* October 14, 2024. Accepted in final form December 23, 2024. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

References

1. Alcalá-González LG, Malagelada C. Current insights on chronic intestinal dysmotility: pseudo-obstruction and enteric dysmotility. *Rev Esp Enferm Dig*. 2024;116(2):63-67. doi:10.17235/REED.2023.10038/2023
2. Blackburn KM, Kubiliun M, Harris S, Vernino S. Neurological autoimmune disorders with prominent gastrointestinal manifestations: a review of presentation, evaluation, and treatment. *Neurogastroenterol Motil*. 2019;31(10):e13611. doi:10.1111/nmo.13611
3. Malagelada C, Karunaratne TB, Accarino A, et al. Comparison between small bowel manometric patterns and full-thickness biopsy histopathology in severe intestinal dysmotility. *Neurogastroenterol Motil*. 2018;30(3). doi:10.1111/NMO.13219
4. Nakane S, Higuchi O, Koga M, et al. Clinical features of autoimmune autonomic ganglionopathy and the detection of subunit-specific autoantibodies to the ganglionic acetylcholine receptor in Japanese patients. *PLoS One*. 2015;10(3):e0118312-e0118319. doi:10.1371/journal.pone.0118312
5. Anderson NE, Hutchinson DO, Nicholson GJ, Aitchison F, Nixon JM. Intestinal pseudo-obstruction, myasthenia gravis, and thymoma. *Neurology*. 1996;47(4):985-987. doi:10.1212/wnl.47.4.985
6. Trewin BP, Freeman I, Ramanathan S, Irani SR. Immunotherapy in autoimmune encephalitis. *Curr Opin Neurol*. 2022;35(3):399-414. doi:10.1097/WCO.0000000000001048
7. Bastiaansen AEM, De Jongste AHC, De Bruijn MAAM, et al. Phase II trial of natalizumab for the treatment of anti-Hu associated paraneoplastic neurological syndromes. *Neurooncol Adv*. 2021;3(1):vdab145. doi:10.1093/noajnl/vdab145
8. Pang X, He X, Qiu Z, et al. Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2023;8(1):1. doi:10.1038/s41392-022-01259-6
9. Rakocevic G, Barohn R, McVey AL, et al. Myasthenia gravis, thymoma, and intestinal pseudo-obstruction: a case report and review. *J Clin Neuromuscul Dis*. 2003;5(2):93-95. doi:10.1097/00131402-200312000-00004
10. Flanagan EP, Saito YA, Lennon VA, et al. Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. *Neurogastroenterol Motil*. 2014;26(9):1285-1297. doi:10.1111/nmo.12391
11. Rossi S, Merli E, Rinaldi R, et al. Paraneoplastic vs. non-paraneoplastic anti-Hu associated dysmotility: a case series and literature review. *J Neurol*. 2022;269(3):1182-1194. doi:10.1007/s00415-021-10577-8
12. Coret F, Bosca I, Fratalia L, Perez-Griera J, Pascual A, Casanova B. Long-lasting remission after rituximab treatment in a case of anti-Hu-associated sensory neuronopathy and gastric pseudoobstruction. *J Neurooncol*. 2009;93(3):421-423. doi:10.1007/S11060-008-9787-Y
13. Badari A, Farolino D, Nasser E, Mehboob S, Crossland D. A novel approach to paraneoplastic intestinal pseudo-obstruction. *Support Care Cancer*. 2012;20(2):425-428. doi:10.1007/S00520-011-1305-7
14. Drukker CAM, Heij HA, Wijnaendts LCD, Verbeke JIML, Kaspers GJL. Paraneoplastic gastro-intestinal anti-Hu syndrome in neuroblastoma. *Pediatr Blood Cancer*. 2009;52(3):396-398. doi:10.1002/PBC.21807
15. De Schamphelaere E, Sieben A, Heyndrickx S, Lammens M, Geboes K, De Bleecker JL. Long lasting trigeminal neuropathy, limbic encephalitis and abdominal ganglionitis without primary cancer: an atypical case of Hu-antibody syndrome. *Clin Neurol Neurosurg*. 2020;194:105849. doi:10.1016/J.CLINNEURO.2020.105849