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LETTER TO THE EDITORS

High-dose immunoglobulin pulse therapy and risk of Covid19 infection

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Dear Sirs,

COVID-19 emerged as a novel disease at the beginning of 2020 and leads to acute respiratory syndrome. There is no vaccine or specific therapy available. Interestingly, therapy with hyperimmune plasma from recovered COVID-19 patients has been suggested as a possible therapeutic approach [1]. Intravenous immunoglobulins (IVIg) may harbour some protective effect, even in the absence of direct contact by donors with the infective agent [2].

We focused our study on patients affected by immune-mediated neuromuscular diseases [3]. The majority of them are chronically treated with a high dosage of IVIg or subcutaneous (SCIg) immunoglobulins, giving us the opportunity of evaluating a large number of subjects and compare the results with a control group represented by patients with the same diseases following other immunomodulatory therapies.

IVIg produced before the H1N1 influenza pandemic, avoid the lung replication of the virus, and protect against mortality because of a cross-reaction of the antibody to this virus [2]. Hemagglutinin and neutralising antibodies against pandemic influenza have been found in IVIg and they have a protective effect from H1N1 infection. IVIg effectively inhibit the replication of HCoV-NL63, a coronavirus which leads to acute respiratory syndrome in adults and to Kawasaki disease in children, similar to SARS-CoV-2, so that commercially available immunoglobulins may represent a potential therapy for treating acute respiratory illness [4]. Moreover, pre-pandemic IVIg can provide protection by a mechanism of antibodies cross-reaction induced by repeated exposure to seasonal H1N1 or coronaviruses, and hyperimmune post-pandemic IVIg may be more effective in protecting the host, as demonstrated in mice [5].

To address the potential protective effect of IVIg against COVID-19 infection, even if obtained before the pandemic, we conducted, through the CIDP Italian Association, an online anonymous questionnaire among patients affected by immune-mediated neuromuscular diseases, from 4 to 28 April. In this population, we assessed possible COVID-19 infection and the effects of other immunosuppressive therapies. We chose an online questionnaire due to the impossibility of reaching all the patients because of the lockdown and in order to collect a high number of subjects in a fast way. This method has obviously different limitations, first of all, we could contact only the patients afferent to the association or to outpatients' hospital facilities and thus only patients with an ongoing therapy. Therefore, we could not recruit patients with previous diseases and without therapy. Anyway, considering the limitation of the lockdown the online questionnaire was the only way to conduct a survey. 213 patients participated in the survey, but we had to exclude two

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incomplete questionnaires. The majority of patients suffered from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP, 73.9%; *n*: 156), followed by other immune-mediated neuromuscular diseases. In this population, 46% did not report any comorbidities, 35.5% had one comorbidity and only a minority had more than one comorbidity (14.5%; Table 1). 165 patients were under monthly IVIg treatment or SCIg. The others (*n*: 46) had different therapies, such as immunomodulatory drugs or no therapy (Table 1). Four patients contracted COVID-19. We excluded patients with general symptoms but without a laboratory confirmation to exclude some evaluation mistakes or biases due to misjudgement by the patients (*n*: 16). Only one was under IVIg therapy and the other three patients were on steroids (*n*: 2) or no therapy (*n*: 1; Table 1). Comparing these data, where patients with no IVIg therapy can be considered a control group, with a Chi-square test and a Yates correction, the difference between these two groups is significant (Chi square: 3.887; degrees of freedom: 1, $p < 0.05$; Table 1). Finally, we observed that the incidence of COVID-19 infection in our selected population is 2%. These data suggest that patients undergoing IVIg or SCIg chronic treatments may have a reduced risk of contracting COVID-19 infection compared to patients receiving other immune therapies or no therapy.

In conclusion, we can hypothesise that, as already demonstrated, chronic immunoglobulin therapy may protect or reduce the risk of contracting infections, including COVID-19. More studies based on medical recording and with a stratification of patients based on type of disease and on degree of severity, are needed to confirm our conclusions, which could possibly be conducted when the COVID-19 emergency ends and access to clinical data and visits will be available again.

Table 1 Resume of data collected

General information		Comorbidities–number (%)	
Total of patients (number)	213	Total	211
Excluded	2	No comorbidities	97 (46)
Patients included	211	One comorbidity	75 (35.5)
Female–number (%)	84 (39.8)	More than one comorbidity	39 (14.5)
Mean age (range)–years	39–79 (52.3)		

Diseases–number (%)		Type of comorbidities–number (%)	
Total	211 (100)	Total	151 (100)
CIDP	156 (73.9)	Respiratory	23 (15.2)
GBS	9 (4.3)	Cardiovascular	45 (29.8)
MMN	31 (14.7)	Dysimmune	17 (11.3)
Myasthenia	6 (2.8)	Neurologic	9 (6)
Anti-MAG antibody neuropathy	7 (3.3)	Metabolic	21 (13.9)
Vasculitis	1 (0.5)	Tumours	5 (3.3)
Parsonage Turner	1 (0.5)	Others	31 (20.5)

Therapy–number (%)		Therapy (total)	Negative	Positive
Total	211 (100)			
IVIg	104 (49.3)	IVIg (95)	90.4% (94)	1% (1)
SCIg	55 (26.1)	SCIg (52)	94.5% (52)	
Steroids	17 (8)	Steroids (17)	88.2% (15)	11.8% (2)
Other therapies	9 (4.3)	Other therapies (7)	77.8% (7)	
No therapy	7 (3.3)	No therapy (7)	85.7% (6)	14.3% (1)
Rituximab	6 (2.8)	Rituximab (5)	83.3% (5)	
IVIg + SCIg	5 (2.4)	IVIg + SCIg (5)	100% (5)	
Azathioprine	4 (1.9)	Azathioprine (4)	100% (4)	
Plasmapheresis	3 (1.4)	Plasmapheresis (2)	66.7% (2)	
Cyclophosphamide	1 (0.5)	Cyclophosphamide (1)	100% (1)	

	Negative	Positive	Chi square, df	*P* value
IVIg, SCIg (152)	92.1% (151)	0.6% (1)	3.887, 1	***0.0487**
Other therapies (43)	85.1% (40)	6.4% (3)		

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Compliance with ethical standards

Conflict of interest We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Ethics approval Data collected were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained by specific questions of the questionnaire from all patients for being included in the study.

References

1. Jawhara S (2020) Could intravenous immunoglobulin collected from recovered coronavirus patients protect against covid-19 and strengthen the immune system of new patients? Int J Mol Sci 21(7):2272
2. Rockman S, Lowther S, Camuglia S et al (2017) Intravenous immunoglobulin protects against severe pandemic influenza infection. EBioMedicine. https://doi.org/10.1016/j.ebiom.2017.04.010
3. Haberman R, Axelrad J, Chen A et al (2020) Covid-19 in immune-mediated inflammatory diseases — case series from New York. N Engl J Med. https://doi.org/10.1056/NEJMc2009567
4. Pyrc K, Bosch BJ, Berkhout B et al (2006) Inhibition of human coronavirus NL63 infection at early stages of the replication cycle. Antimicrob Agents Chemother. https://doi.org/10.1128/AAC.01598-05
5. Hohenadl C, Wodal W, Kerschbaum A et al (2014) Hyperimmune intravenous immunoglobulin containing high titers of pandemic H1N1 hemagglutinin and neuraminidase antibodies provides dose-dependent protection against lethal virus challenge in SCID mice. Virol J. https://doi.org/10.1186/1743-422X-11-70