Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 prevalence and outcomes in patients receiving biologic therapies at an infusion center in New York City

Kaoru Harada *, Hsi-en Ho, Charlotte Cunningham-Rundles

Division of Allergy and Clinical Immunology, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1468 Madison Ave, New York, NY 10029, USA

ARTICLE INFO

Keywords:
COVID-19
Immunodeficiencies
Immunomodulatory therapy
Biologic therapy

ABSTRACT

To better understand COVID-19 infection in patients receiving biologic and immunomodulatory therapies, we evaluated prevalence and outcomes for symptomatic cases of COVID-19 at a large therapeutic infusion center in New York City during the height of the pandemic. 2074 patients received treatment with biologic infusions at our center between March and May 2020, and 34 patients developed symptomatic COVID-19 infection, for an overall low rate of 1.64%. The majority of infections and deaths were in a small subset of patients with a primary immunodeficiency. Patients with inflammatory or autoimmune conditions requiring biologic therapies tended to have mild cases. Higher inflammatory responses were observed in patients who died.

1. Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with severe disease characterized by immunological misfiring (1). Data on SARS-CoV-2 infection and outcomes in individuals with immune defects, including those with primary immunodeficiency due to genetic causes or secondary immunosuppression related to immunomodulatory therapies, remain limited. While there is concern that immunomodulatory treatments may negatively affect the clinical outcome, in some cases, selected biologics may protect against a virally provoked cytokine storm associated with severe forms of COVID-19 (2,3).

Between March and May 2020, New York City was the epicenter of the SARS-CoV-2 pandemic (4). At the Mount Sinai Hospital in New York City, over 2000 individuals were receiving treatment at the therapeutic infusion center for primary immunodeficiency or ongoing immunomodulatory therapies during this period. We describe the clinical features and outcomes of symptomatic and PCR-confirmed SARS-CoV-2 infections in this large patient cohort during the height of the pandemic.

2. Materials and methods

2.1. Subjects

Between March 1 and May 30, 2020, 2074 patients were being treated at the Mount Sinai Therapeutic Infusion Center with biologic agents. Patients with symptoms of COVID-19 infection confirmed by positive nucleic acid amplification from nasopharyngeal swab were identified. Electronic health records were queried to identify patient characteristics and comorbidities, including age, sex, body mass index (BMI), race and related comorbidities such as cancer, diabetes, heart disease, hypertension, lung disease and chronic kidney disease (CKD), as well as COVID-19 clinical course and outcome.

2.2. Statistics

Differences in patients who became infected were compared between those requiring hospitalization versus only outpatient management, using contingency table chi-square analysis and two-sided t-test for categorical and continuous variables, respectively. Individual biomarker data were also collected and included the following: c-reactive protein (CRP), fibrinogen, d-dimer, IL-6, IL-8, TNF-α and IL-1β. Comparison among patients who recovered versus those that expired was performed using Mann-Whitney analysis. All statistical analysis was performed using STATA software (StataCorp, College Station, TX, USA).

* Corresponding author.
E-mail addresses: kaoru.harada@mssm.edu (K. Harada), hsi-en.ho.mountsinai.org (H.-e. Ho), charlotte.cunningham-rundles@mssm.edu (C. Cunningham-Rundles).

https://doi.org/10.1016/j.clim.2021.108803
Received 23 March 2021; Received in revised form 14 July 2021; Accepted 19 July 2021
Available online 21 July 2021
1521-6616/© 2021 Elsevier Inc. All rights reserved.
3. Results

3.1. Patient demographics

Between March 1 and May 30, 2020, a total 2074 patients were being treated at the Therapeutic infusion Center with intermittent biologic or immunomodulatory therapies. Out of 2074 patients, 34 of these patients developed symptomatic infection with COVID-19, for an overall infection rate of 1.64%. Table 1 summarizes the demographic characteristics for these patients, their diagnosis, and the medications being infused. The median age of these patients was 58 years, and 59% (n = 20) of the patients were female. Among patients with symptomatic, PCR-confirmed COVID-19, primary immunodeficiency (PID) was the most common diagnosis for which they were being treated at the Infusion Center (n = 11; common variable immunodeficiency (CVID) (n = 6), hypogammaglobulinemia (n = 2), X-linked agammaglobulinemia (XLA) (n = 2), and IgA-IgG subclass 2 deficiency (n = 1)). Inflammatory bowel disease (n = 7) and multiple sclerosis (n = 7) were the second most common diagnoses. Other diagnoses in our patient population who were infected with COVID-19 were demyelinating neuropathies (n = 2), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy, chronic urticaria (n = 1), giant cell arteritis (n = 1), osteoarthritis (n = 1), myasthenia gravis (n = 1), rheumatoid arthritis (n = 1), systemic lupus erythematosus (n = 1), and kidney transplant (n = 1).

3.2. Biologic and immunomodulatory infusions

The 34 patients diagnosed with COVID-19 were receiving intermittent infusions of intravenous immunoglobulin (IVIG), infliximab, natalizumab, ocrelizumab, rituximab, vedolizumab, tocilizumab, belatacept, denosumab, and omalizumab (Table 2). Between March 1 and May 30, 3277 infusions of these biologics were administered to 1745 patients. In total, 4137 biologic infusions were administered to 2074 patients during this time. The other biologic agents infused in this time period with no cases of symptomatic COVID-19 included other TNF-α inhibitors (certolizumab, golimumab), anti-IL-5 therapy (benralizumab, mepolizumab, reslizumab), abatacept, belimumab, til-dakizumab, ustekinumab, and zinplava.

3.3. Clinical outcomes in patients with PID

Between March and May, 128 individual patients with PID were being treated at the infusion center for IVIG. Eleven patients with PID on IVIG developed symptomatic and PCR-confirmed COVID-19 infection. Ten of the 11 patients diagnosed with COVID-19 were admitted. Five patients required supplemental oxygen by nasal canula and were discharged home. One patient with XLA was admitted but did not require supplemental oxygen.

Four patients were admitted to the ICU, required ventilation, and died. Of these 4 patients, 2 patients had CVID, 1 patient had hypogammaglobulinemia, and 1 patient had IgA and IgG subclass deficiency. All four of these patients had additional co-morbidities, including complications associated with immunodeficiency. The first patient with CVID had a history of bronchiectasis, immune thrombocytopenic purpura, and splenectomy and had recently received rituximab. The second patient with CVID had a medical history that was notable for systemic lupus erythematosus, kidney transplant due to lupus nephritis, and malignancy; she was on chronic prednisone. The one patient with hypogammaglobulinemia had coronary artery disease, heart failure, chronic kidney disease, type 2 diabetes mellitus, and chronic obstructive pulmonary disease (COPD). The patient with IgA and IgG subclass deficiency had type 2 diabetes and autoimmune hemolytic anemia (AIHA). He had received prednisone and rituximab in the past for AIHA but had not required recent treatment. The 2 patients with CVID and the patient with IgA and IgG subclass deficiency had symptoms for one week prior to admission and confirmatory testing. The patient with hypogammaglobulinemia had symptoms for 2 days before she presented to the hospital and got tested. Two of the patients had been living with someone with a confirmed case of COVID-19 prior to admission. In regards to treatment, all four patients were treated with hydroxychloroquine. Three of the four patients also received steroids and azithromycin. Two patients received tocilizumab.

3.4. Clinical outcomes in patients receiving immunomodulatory therapy

The number of symptomatic COVID-19 cases for each infusion relative to the total number of people receiving that infusion between March and May are outlined in Table 2. The highest percent of subjects who developed COVID-19 was seen in patients receiving tocilizumab (13.3%), although overall number of patients receiving this medication in this time period was low, at 15 patients. The 2 patients on tocilizumab were getting this infusion for giant cell arteritis. Both of the patients were admitted and survived. Infliximab had the lowest rate; 4 out of 680 patients developed symptomatic COVID-19, for a prevalence of 0.59%. The 4 patients were receiving infliximab for IBD, and all patients were treated as outpatients and survived. Three of the 4 patients did not get any medications prescribed, while one patient was prescribed hydroxychloroquine and azithromycin. The other 3 patients with IBD were receiving treatment with vedolizumab, which also had a low COVID-19 rate of 0.33%. 2 of the 3 patients were admitted; one patient was managed as an outpatient with no medications. All 3 patients survived. With regards to MS treatment, prevalence of infection was 3.33% and 2.14% for natalizumab and ocrelizumab, respectively. All patients with MS survived. One patient on ocrelizumab was admitted and did not

---

**Table 1**

| Demographics | Total (n = 34) |
|--------------|---------------|
| Age (median) | 58 years      |
| Sex          |               |
| Male         | 14 (41%)      |
| Female       | 20 (59%)      |
| Race         |               |
| White        | 14 (41%)      |
| Black        | 7 (21%)       |
| Unknown      | 13 (38%)      |
| BMI (median) | 28.3          |
| Main diagnosis for infusion | Infusion |
| Primary immunodeficiency disease | IVIG (n = 11), Rituximab (n = 1) |
| CVID         | 6             |
| Hypogammaglobulinemia | 2 |
| XLA          | 2             |
| IgA/IgG2 deficiency | 1 |
| IBD (UC, CD) | 7 (21%)       |
| Multiple Sclerosis | 7 (21%)       |
| Demyelinating neuropathy (CIDP, MMN) | 2 (6%) |
| Chronic urticaria | 1 (3%)       |
| Giant Cell Arteritis | 1 (3%)       |
| Osteoarthritis | 1 (3%)       |
| Myasthenia Gravis | 1 (3%)       |
| Rheumatoid Arthritis | 1 (3%)      |
| SLE           | 1 (3%)        |
| Renal Transplant | 1 (3%)      |

**Table 2**

| Infusion | Number (n) |
|----------|------------|
| IVIG (n = 11) |          |
| Rituximab (n = 1) |          |
| Infliximab (n = 4) |          |
| Vedolizumab (n = 3) |          |
| Natalizumab (n = 4) |          |
| Ocrelizumab (n = 3) |          |
| IVIG (n = 1) |          |
| Rituximab (n = 1) |          |
| Tocilizumab (n = 1) |          |
| Omalizumab (n = 1) |          |
| Tocilizumab (n = 1) |          |
| Denosumab (n = 1) |          |
| IVIG (n = 1) |          |
| Tocilizumab (n = 1) |          |
| IVIG (n = 1) |          |
| Belatacept (n = 1) |          |

CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinemia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; MS, multiple sclerosis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; GCA, giant cell arteritis; OA, osteoarthritis; MG, myasthenia gravis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IVIG, intravenous immunoglobulin.
require oxygen supplementation, while none of the other 6 patients with MS were hospitalized. In the 6 patients who did not require admission, 5 of them did not get any medications prescribed. One patient on ocrelizumab was prescribed hydroxychloroquine. Three patients getting rituximab were diagnosed with COVID-19, for a rate of 3.23%. The 3 patients were receiving rituximab for treatment of systemic lupus erythematosus (SLE), myasthenia gravis, and autoimmune complications (thrombocytopenia) from CVID ($n = 1$ for each); these three patients were also receiving IVIG. The patient with SLE did not require admission but no supplementary oxygen. The patient with myasthenia gravis required admission and patients who were treated as outpatients.

### 3.5. Co-morbidities and inflammatory markers

Patient characteristics were compared between patients who required admission and patients who were treated as outpatients. Admitted patients were older and had additional co-morbidities (cancer, diabetes, heart disease, hypertension, lung disease, and CKD). Statistically significant differences were seen for age, hypertension, and CKD ($p = 0.04$, 0.03, and 0.04, respectively). Fourteen of the 20 admitted patients had systemic inflammatory markers (CRP, fibrinogen, d-dimer, IL-6, IL-8, TNF-α, IL-1β) tested during their hospitalization. All inflammatory markers were higher in patients who died, with statistically significant differences found in CRP, d-dimer, and IL-6 ($p = 0.03$, 0.004, 0.047, respectively). Treatments that are currently under investigation, such as glucocorticoids and immunomodulatory therapies, were not yet used at this early stage in the pandemic. Five patients received steroids while they were admitted, and 4 of them died. Two PID patients were treated with tocilizumab and did not survive, as discussed in section 3.3.

### 4. Discussion

Overall, there was a low rate of symptomatic COVID-19 cases of 1.64% at this NYC infusion center, which treated 2074 patients between March 1 and May 30, 2020 with intermittent biologic or immunomodulatory therapies. While it is possible that more patients had asymptomatic COVID-19, especially during this period when testing was greatly limited, our data provides further insight into the clinical course and outcome of this unique patient population when NYC was the epicenter of the pandemic.

The majority of infections and deaths were in a small subset of patients with a primary immune defect. Patients with PID accounted for only 128 of the 2074 total patients treated at the infusion center during those three months, while nearly a third of the symptomatic and confirmed COVID-19 cases were in our PID patient population. A recent study at our institution’s Immune Deficiency center found that COVID-19 symptoms in this patient population ranged from mild illness to death; in this study, mortality rates were greater than the general population in NYC (25% compared to 10.2%), and poorer outcomes were associated with preexisting autoimmune complications and other comorbidities such as lung disease (5). A multicenter, retrospective international study evaluating SARS-CoV-2 infection in patients with inborn errors of immunity found that case fatality rate and risk factors for severe disease (pre-existing heart, lung, or kidney disease) were similar to those in the general population (6).

While the great majority of patients treated at the infusion center have inflammatory or autoimmune conditions requiring biologics, fewer of these patients developed symptomatic COVID-19, and they had relatively mild cases. Out of the 7 patients with IBD receiving vedolizumab or infliximab who developed COVID-19, 2 were admitted and all survived. Patients with MS who became infected had similarly favorable outcomes. Of the 7 patients receiving natalizumab or ocrelizumab, only one patient was admitted, and there were no deaths. In comparison, fatality rate was 9.2% overall and 32.1% among hospitalized patients in NYC during this time period (4). Our findings are consistent with other studies suggesting that patients with autoimmune or inflammatory diseases who require immunomodulators, including IBD and MS, do not appear to have worse outcomes when infected with this virus, as compared to the general public (7–9). A study by the Dutch MS task force did not show worse outcomes in MS patients on immunomodulator therapies, and worse outcomes were associated with known risk factors such as age and comorbidities (7). A case series from New York City evaluating patients with IBD who had confirmed or highly suspected COVID-19 found that hospitalization and mortality rates in this patient population were consistent with those reported in the general population (8). The low incidence of COVID-19 and favorable outcomes from our study reinforce the view that such patients should not terminate immunomodulatory therapies during the current pandemic.

Cytokine storm syndrome has been associated with disease severity and death from COVID-19 (10,11). Elevated acute-response cytokines (TNF and IL-1β) and chemotactic cytokines (IL-8 and MCP-1) lead to increased levels of IL-6, which sustains the inflammatory process via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway (12). Among patients with inborn errors of immunity who were infected with SARS-CoV-2, patients with dominant negative STAT3 variants were found to have mild or asymptomatic disease.

---

### Table 2

| Infusion Diagnosis for infusion | COVID19 cases | Total number of people receiving infusion | COVID-19 rate | Admissions | Deaths | Nasal canula | HFNC, BiPAP | Intubated |
|--------------------------------|--------------|------------------------------------------|---------------|------------|--------|-------------|-------------|-----------|
| IVIG Primary immunodeficiency \(11\) Demyelinating disease \(2\) Secondary immunodeficiency \(1\) SLE \(1\) | 15 | 153 | 9.80% | 13 | 5 | 4 | 1 | 3 |
| Infliximab IBD | 4 | 680 | 0.59% | 0 | 0 | 0 | 0 | 0 |
| Natalizumab MS | 4 | 120 | 3.33% | 0 | 0 | 0 | 0 | 0 |
| Ocrelizumab MS | 3 | 140 | 2.14% | 1 | 0 | 0 | 0 | 0 |
| Rituximab Thrombocytopenia SLE | 3 | 93 | 3.23% | 2 | 1 | 0 | 0 | 1 |
| MG | | | | | | | | |
| Vedolizumab IBD | 3 | 323 | 0.93% | 2 | 0 | 1 | 0 | 0 |
| Tocilizumab GCA | 2 | 15 | 13.33% | 2 | 0 | 1 | 0 | 0 |
| Belatacept Renal Transplant | 1 | 69 | 1.45% | 1 | 0 | 0 | 0 | 0 |
| Denosumab OA | 1 | 39 | 2.56% | 1 | 0 | 0 | 0 | 0 |
| Omalizumab Chronic urticaria | 1 | 79 | 1.27% | 0 | 0 | 0 | 0 | 0 |

HFNC, high flow nasal canula; BiPAP, bilevel positive airway pressure.
suggested that IL-6/STAT3 contributes to the inflammatory response seen in severe cases (6). Several studies have examined the role of inflammatory cytokines on disease course; in particular, IL-6 and TNF-α have been found to be strong predictors of poor outcome, suggesting that they may be potential therapeutic targets (13–15). Our study also found that patients who died from COVID-19 had higher levels of cytokines. In our 4 patients on infliximab, there were no admissions nor have been found to be strong predictors of poor outcome, suggesting that IL-6/STAT3 contributes to the inflammatory response seen in severe cases (6). Several studies have examined the role of inflammatory cytokines on disease course; in particular, IL-6 and TNF-α inhibitors (certolizumab and golimumab). Both COVID-19 patients on tocilizumab who were admitted survived. These findings highlight the importance of ongoing studies investigating IL-6 and TNF-α as potential targets for treatment in severe COVID-19. A recent randomized trial in critically ill patients in the ICU found that treatment with IL-6 receptor antagonists tocilizumab and sarilumab within 24 h of organ support had improved outcomes, including survival and organ support-free days (16). Further studies are needed to evaluate the safety, efficacy, and optimal timing of initiating these therapies in severe COVID-19.

5. Conclusion

Our report highlights a low incidence of symptomatic COVID-19 at a large biologic infusion center during the height of the pandemic in NYC. The majority of admissions and deaths were in patients with PID. Patients who required hospitalization tended to have additional comorbidities, and higher inflammatory markers were observed in patients who died. Further studies on COVID-19 in patients receiving immunomodulators are needed to evaluate safety of continuing therapy during the pandemic, as well as to shed light on potential therapeutic targets for hyperinflammation in severe COVID-19.

Funding

This work was supported by National Institutes of Health [AI 101093, AI-086037, AI-48693] and the David S Gottesman Immunology Chair.

Acknowledgements

The authors would like to thank the staff at the Mount Sinai Therapeutic Infusion Center who assisted with data collection. We are grateful for Dr. Dushyanth Srinivasan’s help in statistical analysis.

References

[1] C. Lucas, P. Wong, J. Klein, T.B.R. Castro, J. Silva, M. Sundaram, et al., Longitudinal analyses reveal immunological misfiring in severe COVID-19, Nature. 584 (7821) (2020) 463–469.
[2] C. Bezzio, L. Pellegrini, G. Manes, I. Arena, D. Piccaccia, C. Della Corte, et al., Biologic therapies may reduce the risk of COVID-19 in patients with inflammatory bowel disease, Inflamm. Bowel Dis. 26 (10) (2020) e107–e91.
[3] F.S. Macaluso, A. Orlando, Could patients with inflammatory bowel disease treated with immunomodulators or biologics be at lower risk for severe forms of COVID-19? Gastroenterology 160 (5) (2020) 1877–1878.
[4] C.N. Thompson, J. Baumgartner, C. Pichardo, B. Toro, L. Li, R. Arcisolo, et al., COVID-19 outbreak - new york City, February 29–June 1, 2020, MMWR Morb. Mortal. Wkly Rep. 69 (46) (2020) 1725–1729.
[5] H.E. Ho, S. Mathew, M.J. Peluso, C. Cunningham-Rundles, Clinical outcomes and features of COVID-19 in patients with primary immunodeficiencies in New York City, J Allergy Clin Immunol Pract 9 (1) (2021) 490–493 (e2).
[6] I. Meyts, G. Buccioli, L. Quinti, B. Neven, A. Fischer, E. Seoane, et al., Coronavirus disease 2019 in patients with inborn errors of immunity: an international study, J. Allergy Clin. Immunol. 147 (2) (2021) 520–531.
[7] F.C. Loonstra, E. Hoitsma, Z.L. van Kempen, J. Killestein, J.P. Mostert, COVID-19 in multiple sclerosis: the Dutch experience, Mult. Scler. 26 (10) (2020) 1256–1266.
[8] J.E. Axelrad, L. Malter, S. Hong, S. Chang, B. Bosworth, D. Hudesman, From the American epicenter: coronavirus disease 2019 in patients with inflammatory bowel disease in the New York City metropolitan area, Inflamm. Bowel Dis. 27 (5) (2020) 662–666.
[9] R. Haberman, J. Axelrad, A. Chen, R. Castillo, D. Yan, P. Izmirly, et al., Covid-19 in immune-mediated inflammatory diseases - case series from New York, N. Engl. J. Med. 383 (1) (2020) 85–88.
[10] M. Merad, J.C. Martin, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages, Nat. Rev. Immunol. 20 (6) (2020) 355–362.
[11] B. Hu, S. Huang, L. Yin, The cytokine storm and COVID-19, J. Med. Virol. 93 (1) (2020) 250–256.
[12] S. Bhaskar, A. Sinha, M. Banach, S. Mittor, R. Weissert, J.S. Kass, et al., Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper, Front. Immunol. 11 (2020) 1648.
[13] D.M. Del Valle, S. Kim-Schulze, H.H. Huang, N.D. Beckmann, S. Niremberg, B. Wang, et al., An inflammatory cytokine signature predicts COVID-19 severity and survival, Nat. Med. 26 (10) (2020) 1636–1642.
[14] Z. Hu, S. Li, X. Song, Cytokine storm with rapidly elevated interleukin-6 indicates sudden death in patients with critical COVID-19, Cytokine Growth Factor Rev. 58 (2020) 30–31.
[15] M. Feldmann, R.N. Maini, J.N. Woody, S.T. Holgate, C. Della Corte, et al., Longitudinal analyses reveal immunological misfiring in severe COVID-19, Nature. 584 (7821) (2020) 463–469.
[16] REMAP-CAP Investigators, A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, et al., Interleukin-6 receptor antagonists in critically ill patients with COVID-19, N. Engl. J. Med. 384 (16) (2021) 1491–1502.