Concise Communication

Surveillance of adverse drug events associated with tocilizumab in hospitalized veterans with coronavirus disease 2019 (COVID-19) to inform patient safety and pandemic preparedness

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Abstract

We evaluated adverse drug events (ADEs) by chart review in a random national sample of 428 veterans with coronavirus disease 2019 (COVID-19) who received tocilizumab (n = 173 of 428). ADEs (median time, 5 days) occurred in 51 of 173 (29%) and included hepatotoxicity (n = 29) and infection (n = 13). Concomitant medication discontinuation occurred in 22% of ADE patients; mortality was 39%.

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The rapid dissemination of practice patterns for coronavirus disease 2019 (COVID-19) underscores the need for ongoing critical safety and efficacy surveillance of off-label treatments. The Department of Veterans Affairs conducts a safety surveillance program to track the safe and appropriate use of off-label treatments for veterans with COVID-19, including those approved under emergency use authorization (EUA). Tocilizumab, a monoclonal antibody to the IL-6 receptor, has been used as an off-label treatment for hospitalized patients with moderate-severe COVID-19.1,2 Methods of posttreatment surveillance are needed to weigh the benefits and harms of off-label treatments such as tocilizumab, particularly while randomized controlled trials are ongoing. There are limited reports of adverse drug events (ADEs) and subsequent unfavorable outcomes associated with tocilizumab.3 The Veterans Health Administration (VHA), with 170 medical centers across 22 geographic regions, offers an ideal setting to inform models of posttreatment surveillance. We characterized ADEs associated with tocilizumab using a random national sample of inpatients with COVID-19 across the VHA.

Methods

We conducted a retrospective evaluation of patients ≥18 years of age with COVID-19 who were hospitalized between March 12, 2020, and August 31, 2020, in the VHA. We identified the subset of patients who received ≥1 dose of tocilizumab during hospitalization. Randomized controlled trials evaluating the safety and efficacy of tocilizumab in COVID-19 patients were not enrolling VHA patients during the evaluation; patients received tocilizumab at the discretion of their clinicians. Exposure to tocilizumab was ascertained through the electronic health record and confirmed on chart review. This project was approved under the Drug Use Evaluation project by the VHA Institutional Review Board.

Among all inpatients prescribed tocilizumab for COVID-19–associated diagnoses during the evaluation period, we selected a 40% sample of patients using simple random sampling. For all patients in the sample, we collected demographic, comorbidity, hospitalization, laboratory, and tocilizumab administration data by database extraction and confirmed these data via chart review. We ascertained whether patients were prescribed concomitant medications to manage COVID-19. We also obtained data related to the presence of symptoms associated with COVID-19, receipt of critical care, need for mechanical ventilation, and exposure to risk factors for COVID-19.

The primary outcome was the proportion of patients with an ADE temporally associated with tocilizumab administration. ADEs included injection site reactions, neutropenia, thrombocytopenia, anaphylaxis, hepatotoxicity, gastrointestinal perforation, elevated triglycerides, and new infections (tuberculosis, candidemia, bacteremia, varicella zoster, and other infections).3 Trained clinical pharmacist specialists used standardized definitions to evaluate ADEs (Supplementary Table 1 online) among equitable samples of patients. Among patients who developed ADEs, secondary outcomes of ADE severity were characterized as

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Table 1. Characteristics of Patients Hospitalized With COVID-19 Who Received Tocilizumab at Veterans Health Administration Medical Centers (n=173 veterans from 43 centers)

| Characteristic                              | 3/12–8/31/20 (N = 173), No. (%) | 3/12–5/31/20 (N = 117), No. (%) | 6/1–8/31/20 (N = 55), No. (%) |
|---------------------------------------------|---------------------------------|---------------------------------|--------------------------------|
| **Age, y (SD)**                             |                                 |                                 |                                |
| 18 to <35                                   | 1 (1)                           | 1 (1)                           | 0 (0)                          |
| 35 to <55                                   | 27 (16)                         | 18 (15)                         | 8 (15)                         |
| 55 to <75                                   | 105 (61)                        | 74 (63)                         | 31 (56)                        |
| ≥75                                         | 40 (23)                         | 24 (21)                         | 16 (29)                        |
| **Sex, male**                               |                                 |                                 |                                |
| Race                                        |                                 |                                 |                                |
| White                                       | 61 (35)                         | 39 (33)                         | 22 (40)                        |
| Black                                       | 54 (31)                         | 41 (35)                         | 13 (24)                        |
| Other                                       | 5 (3)                           | 5 (4)                           | 0 (0)                          |
| **Comorbidities**                           |                                 |                                 |                                |
| Cardiovascular disease                      | 25 (14)                         | 41 (35)                         | 25 (45)                        |
| Diabetes                                    | 25 (14)                         | 52 (44)                         | 25 (45)                        |
| Pulmonary disease                           | 14 (8)                          | 35 (30)                         | 14 (25)                        |
| Immunocompromised                           | 7 (4)                           | 6 (5)                           | 7 (13)                         |
| **Presenting symptoms of COVID-19**         |                                 |                                 |                                |
| Cough                                       | 125 (72)                        | 84 (72)                         | 40 (73)                        |
| Fever                                       | 121 (70)                        | 87 (74)                         | 33 (60)                        |
| Dyspnea                                     | 118 (68)                        | 79 (68)                         | 38 (69)                        |
| Myalgia or fatigue                          | 86 (50)                         | 60 (51)                         | 26 (47)                        |
| Altered mental status                       | 10 (6)                          | 7 (6)                           | 3 (5)                          |
| Chest pain                                  | 6 (3)                           | 2 (2)                           | 4 (7)                          |
| Other                                       | 84 (49)                         | 58 (50)                         | 26 (47)                        |
| **Risk factors for COVID-19**               |                                 |                                 |                                |
| Exposure to community transmission          | 92 (53)                         | 60 (51)                         | 32 (58)                        |
| Healthcare profession                       | 6 (3)                           | 5 (4)                           | 1 (2)                          |
| International travel                        | 1 (1)                           | 0 (0)                           | 1 (2)                          |
| Other                                       | 10 (6)                          | 6 (5)                           | 4 (7)                          |
| **Hospital length of stay, d**              |                                 |                                 |                                |
| 1 to <3                                     | 1 (1)                           | 1 (1)                           | 0 (0)                          |
| 3 to <7                                     | 10 (6)                          | 7 (6)                           | 2 (4)                          |
| 7 to <14                                    | 38 (22)                         | 29 (25)                         | 9 (16)                         |
| ≥14                                         | 108 (62)                        | 68 (58)                         | 40 (73)                        |
| Intensive care unit admission               | 155 (90)                        | 104 (89)                        | 51 (93)                        |
| Receipt of mechanical ventilation           | 105 (61)                        | 76 (65)                         | 29 (53)                        |
| **Discharge disposition**                   |                                 |                                 |                                |
| Home                                        | 68 (39)                         | 42 (36)                         | 25 (45)                        |
| Rehabilitation/Skilled nursing facility     | 17 (10)                         | 13 (11)                         | 4 (7)                          |
| Died                                        | 69 (40)                         | 48 (41)                         | 21 (38)                        |

(Continued)
Efficient and comprehensive surveillance of off-label treatments for COVID-19 is necessary to identify opportunities to improve patient safety among hospitalized patients. We evaluated ADEs associated with tocilizumab to inform a potential framework for the real-time assessment of the safety of off-label treatments used among VHA inpatients with COVID-19. Using a random national sample, nearly 30% developed ADEs, and ADEs often led to discontinuation of concomitant medications. Hospital mortality did not vary by the development of ADEs. Collectively, our findings support hospital epidemiology and antimicrobial stewardship programs that are charged with promoting patient safety, pandemic preparedness, and, increasingly, institutional treatment protocols for COVID-19.

The Sentinel Initiative led by the Food and Drug Administration includes the largest multicenter database in the world dedicated to medical product safety, and collaborative efforts with VHA inform safety surveillance efforts in the largest integrated healthcare system in the United States. It is important to conduct surveillance in this population because VHA patients may be at increased risk of ADEs due to the prevalence of advanced age, multimorbidity, and disparities in COVID-19 burden. By conducting rigorous chart reviews using standardized definitions in a random sample of nationwide inpatients, our work offers a potential approach to evaluate the safety of off-label treatments for COVID-19 in close to real-time within VHA and general populations of older adults with multimorbidity. This approach presents opportunities to improve safety among hospitalized veterans with COVID-19 and helps capture real-world outcomes for patients exposed to off-label treatments, beyond what is typically reported from clinical trials. An additional advantage of this approach using integrated VHA data is the potential to replicate this methodology over time for veteran and nonveteran populations, particularly during subsequent waves of COVID-19 and future pandemics. Developing mechanisms to monitor off-label treatments for emerging infectious diseases across healthcare systems may promote pandemic preparedness.

Our work has limitations. This work was done within a national pharmacy safety surveillance program with the goal of tracking the safe and appropriate use of off-label medications in veterans. Consequently, we could not assess ADEs among all VHA inpatients exposed to tocilizumab. Nevertheless, inpatients were selected randomly, and the sample size is comparable to prior reports. Second, our findings have limited representation of women. Finally, we were not powered to identify predictors of ADE in veterans.

In summary, 29% of patients exposed to tocilizumab developed an ADE during hospitalization. ADEs often involved hepatotoxicity and secondary infections and frequently resulted in discontinuation of concomitant medications. This evaluation provides a potential framework for the real-time assessment of the safety of off-label treatments used for COVID-19 among VHA inpatients and may inform recommendations from hospital epidemiology and antimicrobial stewardship programs.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.227

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