Original Article

ISSN: 1735-0344 *Tanaffos 2024; 23(3): 250-255*

TANAFFOS

Changes in Pharmacological Approach to COVID-19 in a Referral Hospital in Tehran During Two Years

Seyed Mehran Marashian [1,2], Mohsen Sadeghi [1,2], Somayeh Lookzadeh [1], Azadeh Moradkhani [1], Akram Qanavati [1,2], Zeinab Chaghervand [1], Sanaz Soleimani [1], Farnaz Hadipour [1], Maryam Shahmorad [1], Mahboobeh Mohammadi [1], Shirin Esmaeili[1], Latifeh Javadi [1], Hooman Sharifi [3], Esmaeil Idani [1,2], Hamidreza Jamaati [1], Alireza Eslaminejad [1,2]

[1] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Pulmonary Function Research Center , NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran [3] Tobacco Prevention and Control Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 8 April 2023
Accepted: 9 February 2024

Correspondence to: Eslaminejad A
Address: Chronic Respiratory Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: eslaminejadalireza@sbmu.ac.ir

Background: The current study attempts to look at the trend of medication prescription among inpatients with COVID-19 by comparing two groups of them who were admitted into our hospital at separate times at around two-year intervals.

Materials and Methods: Through a retrospective cross-sectional design, the current study enrolled hospitalized cases from two separate periods including winter 2019 and summer 2021 to compare some characteristics of COVID-19 in addition to sex and age distribution as well as the approach and management and their changes as the time passed.

Results: Remdesivir was raised to be the most commonly used medication for COVID-19 after one and a half years when approved by the FDA in this regard. Tocilizumab was prescribed for just less than 6% of earlier pandemics in winter 2019 while used in more than half of hospitalizations in 2021. After two years, corticosteroids are used in 98.6% of the cases at least in our center.

Conclusion: Exact medication administration to target COVID-19 and accurate vaccination in addition to "Herd immunity" among the global population seems to be the chief secret of the current success at least for partial control of the disease now.

Keywords: COVID-19; Remdesivir; Tocilizumab; Corticosteroids; Medications; Management

INTRODUCTION

COVID-19, involving at least 213 countries and territories, emerged in January 2019 to cause a total of 423 million worldwide cases and more than 6 million global deaths up to now. Iran has experienced just less than 7 million COVID-19 cases resulting in 135 thousand deaths as the data shows (1,2). There was a very wide range of different medications prescribed for hospitalized COVID-19 patients regarding the global and national protocols which changed based on new findings and research as time went on. A vast number of anti-viral and anti-bacterial agents came into use which were known active through previous epidemics and pandemics such as H1N1, SARS-CoV, MERS, etc. Medications like oseltamivir (Tamiflu®) and hydroxychloroquine sulfate and later adding lopinavir/ritonavir (also known as "Kaletra®") were raised much more than other medications regarding their effects on severe influenza for the former and malaria control during previous viral pandemics for the second one (3). Nowadays, after about two years of starting the

COVID-19 pandemic, the treatment protocols are changed switching the medications from the named ones to drugs like tocilizumab and remdesiver targeting cytokine storm and viral load as well as many other conditions which push the disease to much more severe types.

The current study attempts to look at the trend of medication prescription among inpatients with COVID-19 by comparing two groups of them who were admitted into our hospital at separate times at around two-year intervals.

MATERIALS AND METHODS

The current study utilized a retrospective cross-sectional design to analyze hospitalized COVID-19 cases from two distinct periods: winter 2019 and summer 2021. The aim was to compare various characteristics of COVID-19, including the distribution of cases by sex and age, as well as the changes in approach and management over time.

This study utilized a registry established for COVID-19 at our referral hospital, which records clinical, laboratory, and radiographic findings for hospitalized patients, respectively.

Subjects

Totally, our center has welcomed more than 6000 COVID cases since the winter of 2019 which needed too much time to be recorded and studied. The current study enrolled 664 cases including 517 from 2019 and 147 from 2021. All of the patients were studied for clinical, laboratory, and radiographic presentations. The study protocol was approved by the local ethics committee at the coordinating center (Shahid Beheshti University of Medical Science) (IR.SBMU.NRITLD.REC.1401.036) and has been performed following the ethical standards laid down in the 2000 Declaration of Helsinki.

Clinical information

All of the patients had referral codes to be found in a huge information pool in our tertiary referral university hospital by which we found scanned records to export necessary information including demographics, disease manifestations, general condition, comorbidities, impression and diagnosis, ordered medications, nursing reports, vital sign charts, and more. The outcomes of hospitalization such as death, ICU admission, and discharge in good condition were found as well.

Laboratory findings

There is a bank for laboratory records of the patients, using which we gathered many items from blood group and biochemistry, serum concentrations of inflammatory markers such as interleukins, D-dimer, ESR, CRP, etc., real-time PCR results for COVID-19, and blood cell count.

Radiographic findings

Using a source named PACS, our referral center records all the radiography, stereotypes, and reports belonging to any radiographic study which was done including plain radiography, CT-scan, MRI, and even PET-scan. Referring to them, we were able to find any CT-scan pattern or finding regarding our variable checklist such as ground-glass opacity (GGO), cavitary lesions, lobar or pleural involvement, and many other signs.

RESULTS

We studied 517 records in the winter of 2019 and compared them with 147 records from the summer of 2021. Of the total patients, 427(64.3%) were males which doubled the female rate. The most found age category was the group of 60 and older patients with evenly reduced rates to younger patients. The two studied time sections had similar age and sex distributions as can be seen in Table 1. The average hospital stay was 8.53±5.57 days and hypertension was the most comorbidity found followed by diabetes mellitus and cardiovascular diseases. Cough and dyspnea were the most common symptoms followed by fever, myalgia, chills, fatigue, and anorexia which had the same trends in two separate studied time sections.

The most prominent issue was the administered medications to treat the disease when compared between the two-time sections evaluated by the current study. Kaletra® (Lopinavir/ritonavir) was the most ordered medication in 2019 in our center along with ceftriaxone and azithromycin followed by hydroxychloroquine and Tamiflu® (oseltamivir phosphate) as found in Table 2.

Table 1. Comparison of findings between 2019 and 2021

		2019 Number (%)	2021 Number (%)	P Value
Age (years)	**Mean ± SD**	55.88 ± 15.43	56.02 ± 16.04	0.921
	15-30	26 (5)	7 (4.8)	
	31-40	66 (12.8)	22 (15)	
	41-50	92 (17.8)	30 (20.4)	
	51-60	137 (26.6)	26 (17.7)	
	≥60	195 (37.8)	62 (42.2)	
Sex	**Male**	340 (65.8)	87 (59.2)	0.142
	Female	177 (34.2)	60 (40.8)	
Outcome	**ICU admission**	171 (33.1)	41 (27.9)	0.270
	Death	79 (15.3)	14 (9.5)	0.076
Smoking		39 (7.5)	11 (7.5)	0.980
Opium consumption		14 (2.7)	2 (1.4)	0.543
Pulmonary disease		57 (11)	8 (5.4)	0.044
Immunocompromised cases		14 (2.7)	4 (2.7)	>0.999
Malignancy		17 (3.3)	4 (2.7)	>0.999
Diabetes Mellitus		144 (27.9)	42 (28.6)	0.864
Hypertension		155 (30)	48 (32.7)	0.535
Cardiovascular diseases		76 (14.7)	23 (15.6)	0.776
Hepatitis		5 (1)	0 (0)	0.592
Fever		349 (67.5)	67 (45.60	<0.001
Cough		408 (78.9)	118 (80.3)	0.721
Dyspnea		407 (78.7)	118 (80.3)	0.684
Chills		176 (34)	43 (29.3)	0.276
Fatigue		62 (12)	28 (19)	0.027
Sore throat		22 (4.3)	4 (2.7)	0.397
Chest pain		29 (5.6)	16 (10.9)	0.025
Vomiting		50 (9.7)	27 (18.4)	0.004
Sputum		55 (10.6)	26 (17.7)	0.021
Anorexia		84 (16.2)	33 (22.4)	0.082
Myalgia		215 (41.6)	66 (44.9)	0.473

Actemra® (Tocilizumab) was prescribed for just less than 6% of the early pandemic in the winter of 2019 while used in more than half of hospitalizations in 2021. Favipiravir, rivaroxaban, remdesivir, and ribavirin were the other antivirals among which remdesivir was raised to be the most commonly used medication for COVID-19 after one and a half years when approved by the FDA in this regard.

Another challengeable medication group was corticosteroids which seemed risky early in the pandemic to be picked up only in very severe conditions to save patients' lives; but now, after two years, are used in just less than 100% of COVID cases (98.6%) at least in our center. hospital stays, ICU admission, sex contribution, manifestation rates, and comorbidities were statistically the same during the two separate time sections we studied.

Table 2. The frequency of administered medications in 2019 and 2021

Year	2019 Number (%) N=517	2021 Number (%) N=147	P Value
Tocilizumab	30 (5.8)	74 (50.3)	< 0.001
Favipiravir	59 (11.4)	6 (4.1)	0.008
Rivaroxaban	9 (1.7)	2 (1.4)	>0.999
Oseltamivir	319 (61.7)	0 (0)	< 0.001
Kaletra	445 (86.1)	0 (0)	< 0.001
Vancomycin	176 (34)	15 (10.2)	< 0.001
HydroxyChloroquine	344 (66.5)	0 (0)	< 0.001
Meropenem	220 (42.6)	8 (5.4)	< 0.001
Remdesivir	32 (6.2)	142 (96.6)	< 0.001
Ribavirin	98 (19)	0 (0)	< 0.001
Ceftriaxone	373 (72.1)	107 (72.8)	0.878
Ofloxacin	98 (19)	12 (8.2)	0.002
Corticosteroid	205 (39.7)	145 (98.6)	< 0.001
Azithromycin	381 (73.7)	41 (27.9)	< 0.001
Methotrexate	5 (1)	0 (0)	0.592

DISCUSSION

The current study tried to compare the approach to COVID-19 and its changes in 2 years to show the challenges of facing a new pandemic in a referral center in Tehran. Despite the statistical pattern of the disease in two years, our study presented the effect of knowledge and experience and their importance through the management of the pandemic which caused worldwide confusion for a while. As explained before, sex and age distribution were the same among our samples from the two separate studied time sections which was not far from the expectations that the disease would be more common and present more severity in older individuals due to weak immunity and body resistance, finally resulting in more hospitalization and unfortunately death rates, especially among complicated cases.

There was a long list of risk factors at first either proved by the WHO or introduced by some experts among which the ABO blood group was the simplest one. The risk

factors are under study yet and nobody can definitely accept or deny them; the issue is a major controversy due to the confusion caused by the disease worldwide. (4-6). However, our study showed no finding in this matter. On the other hand, pulmonary comorbidities were not a serious risk factor for infection which was perhaps the result of more strict care about personal hygiene in that group of people (7,8).

Focusing on the prescribed medications we figured out evolutional changes in approach and management of the disease. Actemra administration, as an IL6 inhibitor, really grew up to 50% after two years compared to 2019 which was ordered only for just less than 6% of the patients. Many studies and authors have introduced interleukin-6 (IL-6) as the crucial cytokine to push patients to ill and critical situations by driving cytokine storm which is the worst event occurring through COVID-19 to exhaust immune system by occupying a vast number of immune factors containing inflammatory and anti-inflammatory ones (9). The named drug, as a monoclonal antibody IL-6 receptor antagonist, is a potential candidate to be approved by the FDA based on its success against cytokine release syndrome which is similar to cytokine storm in COVID-19 (10,11). Antivirals such as Favipiravir, Tamiflu® (oseltamivir), Kaletra®, and Ribavirin almost vanished from the orders after months when specialists and the World Health Organization found them inefficient although many studies gave high credits to them early. Kaletra was one of the most attractive therapies early in the pandemic used pronouncedly in Iran but there was no evidence relating to the benefits despite some pharmacodynamics concerns about achieving drug concentration in the body to inhibit the virus (12-14). Remdesivir was ordered in just more than 6% in 2019 while it was the most common antiviral prescribed for hospitalized patients in summer 2021 (98.6%) as a choice. This medication was finally approved in December 2020 by the Food and Drug Administration (FDA), as the first choice against COVID-19 as an inhibitor of the viral RNA-dependent RNA polymerase to interrupt viral replication (15-18). Remdesivir has a background of antiviral activity against SARS and MERS and studies show noted reduction of lung virus levels and lung damage with the drug in non-human primates. Through later studies, remdesivir presented 31% faster recoveries and around 5% lower death rate with fewer adverse events compared with placebo (19).

One of the biggest challenges of the COVID-19 approach was whether or not to order corticosteroids due to their reciprocal effects. This group of medications may improve a wide range of manifestations at the expense of immunity suppression. So, health providers seriously need to make important and dangerous decisions to support or deny them in severe cases. Corticosteroids could save ill patients from death but might accelerate organ damage by handing over the patients to the disease which would be a serious indiscretion. After lots of efforts to assess the risks and advantages of using corticosteroids, this group of medications came out finally brilliant regarding manifestations improvement and keeping ill patients away from ICU admission and finally death to be used in just less than 100% of hospitalized cases (98.6%) (20,21).

Hydroxychloroquine was the other challengeable medication to use in prophylaxis, and in some cases, treatment of COVID-19. In our center, it was ordered for more than 66% of hospitalized patients in 2019 before being eliminated from the orders in 2021. Hydroxychloroquine was the first recommended medication by the WHO earlier in 2019 not because of its potential for COVID-19 treatment but based on previous experiences of rising malaria mortality in tropical areas in the world through the Ebola pandemic in recent decades. This chiefly led people to use antimalarial drugs although some non-approved effects were seen in COVID-19 prophylaxis and treatment. Although studies reclaim positive effects on symptom improvement, hydroxychloroquine neither reduces the rate of 28-day mortality in COVID-19 nor decreases the need for intubation among the patients while elongating their hospital stay when compared with the standard of care

and the results were the same with or without azithromycin (22,23). Azithromycin had no benefit in the COVID-19 approach in comparison with the standard care in separate studies as well (24).

Remdesivir has been the only FDA-approved choice for COVID-19 up to April 2022. This is while there are strong recommendations against hydroxychloroquine/Chloroquine and/or azithromycin in addition to Kaletra (lopinavir/ritonavir) and other HIV protease inhibitors as well as ivermectin and any interferon in COVID-19 treatment or prophylaxis (25-29). However, remdesivir in combination with corticosteroids, especially dexamethasone, although no direct evidence to prove it, may benefit in severe cases of the disease or patients who need ICU admission due to severe ARDS (30,31).

CONCLUSION

The COVID-19 pandemic presented a two-year challenge, not only in terms of diagnosis and prevention but also in treatment. Treatment approaches varied as new findings emerged about the virus's characteristics worldwide. This prompted governments to allocate significant resources to combat the virus, ultimately leading to improved disease management and efforts to overcome the crisis. Selecting rather right medications against COVID-19 and the right vaccination in addition to "Herd immunity" among the global population seem to be the chief secret of the current success at least for partial control of the disease now.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests

The authors declare no competing interests.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72□314 Cases From the Chinese Center for Disease Control and Prevention. ***JAMA*** 2020;323(13):1239-42.
2. WHO Timeline-COVID-19. Available online at: https://www.who.int/newsroom/detail/08-04-2020-who-timeline---covid-19.
3. Rahmanzade R, Rahmanzadeh R, Hashemian SM, Tabarsi P. Iran's Approach to COVID-19: Evolving Treatment Protocols and Ongoing Clinical Trials. ***Front Public Health*** 2020;8:551889.
4. Ayatollahi AA, Aghcheli B, Amini A, Nikbakht H, Ghassemzadehpirsala P, Behboudi E, et al. Association between blood groups and COVID-19 outcome in Iranian patients. ***Future Virol*** 2021:10.2217/fvl-2021-0090.
5. Nasiri M, Khodadadi J, Hajrezaei Z, Bizhani N. The Probable Association between Blood Groups and Prognosis of COVID-19. ***Iran J Public Health*** 2021;50(4):825-30.
6. Shibeeb S, Khan A. ABO blood group association and COVID-19. COVID-19 susceptibility and severity: a review. ***Hematol Transfus Cell Ther*** 2022;44(1):70-75.
7. Gerayeli FV, Milne S, Cheung C, Li X, Yang CWT, Tam A, et al. COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. ***EClinicalMedicine*** 2021;33:100789.
8. Gallay L, Uzunhan Y, Borie R, Lazor R, Rigaud P, Marchand-Adam S, et al. Risk Factors for Mortality after COVID-19 in Patients with Preexisting Interstitial Lung Disease. ***Am J Respir Crit Care Med*** 2021;203(2):245-9.
9. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ***Proc Natl Acad Sci U S A*** 2020;117(20):10970-5.
10. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. ***N Engl J Med*** 2021;384(16):1503-16.
11. USA Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Drug for Treatment of COVID-19. 24 June 2021. At: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19.
12. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. ***N Engl J Med*** 2020;382(19):1787-99.

13. Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, Khosla PP. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. ***J Infect Public Health*** 2021;14(6):740-748.
14. Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. ***Lancet*** 2020;396(10259):1345-52.
15. Taha HR, Keewan N, Slati F, Al-Sawalha NA. Remdesivir: A Closer Look at Its Effect in COVID-19 Pandemic. ***Pharmacology*** 2021;106(9-10):462-8.
16. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. ***Clin Epidemiol Glob Health*** 2021;9:123-7.
17. Simonis A, Theobald SJ, Fätkenheuer G, Rybniker J, Malin JJ. A comparative analysis of remdesivir and other repurposed antivirals against SARS-CoV-2. ***EMBO Mol Med*** 2021;13(1):e13105.
18. Yin W, Mao C, Luan X, Shen DD, Shen Q, Su H, Wang X, et al. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. ***Science*** 2020;368(6498):1499-504.
19. Bansal V, Mahapure KS, Bhurwal A, Gupta I, Hassanain S, Makadia J, et al. Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis. ***Front Med (Lausanne)*** 2021;7:606429.
20. Ghanei M, Solaymani-Dodaran M, Qazvini A, Ghazale AH, Setarehdan SA, Saadat SH, et al. The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial. ***Respir Res*** 2021;22(1):245.
21. Wagner C, Griesel M, Mikolajewska A, Mueller A, Nothacker M, Kley K, et al. Systemic corticosteroids for the treatment of COVID-19. ***Cochrane Database Syst Rev*** 2021;8(8):CD014963.
22. Chen L, Zhang ZY, Fu JG, Feng ZP, Zhang SZ, Han QY, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. ***Medrxiv*** 2020:2020-06.
23. Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study. ***Am J Trop Med Hyg*** 2020;103(4):1635-9.
24. Chen PH, Jhou HJ, Ou-Yang LJ, Lee CH. Does hydroxychloroquine reduce mortality in patients with COVID-19? A meta-analysis with trial sequential analysis. ***Int J Clin Pract*** 2021;75(10):e14448.
25. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. ***N Engl J Med*** 2022;386(18):1721-31.
26. Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. ***BMC Infect Dis*** 2021;21(1):635.
27. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. ***JAMA*** 2021;325(14):1426-35.
28. Lim SCL, Hor CP, Tay KH, Mat Jelani A, Tan WH, Ker HB, et al. Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. ***JAMA Intern Med*** 2022;182(4):426-35.
29. Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, Khosla PP. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. ***J Infect Public Health*** 2021;14(6):740-8.
30. Béraud G, Timsit JF, Leleu H. Remdesivir and dexamethasone as tools to relieve hospital care systems stressed by COVID-19: A modelling study on bed resources and budget impact. ***PLoS One*** 2022;17(1):e0262462.
31. Marrone A, Nevola R, Sellitto A, Cozzolino D, Romano C, Cuomo G, et al. Remdesivir Plus Dexamethasone Versus Dexamethasone Alone for the Treatment of Coronavirus Disease 2019 (COVID-19) Patients Requiring Supplemental O2 Therapy: A Prospective Controlled Nonrandomized Study. ***Clin Infect Dis*** 2022;75(1):e403-e409.