Prescription profile in patients with SARS-CoV-2 infection hospitalised in Aragon, Spain

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ejhpharm-2020-002476).

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Received 30 July 2020
Revised 19 October 2020
Accepted 2 November 2020
Published Online First 20 November 2020

EAHP Statement 1: Introductory Statements and Governance.

To cite: Alvarez A, Cabia L, Trigo C, *et al*. *Eur J Hosp Pharm* 2022;**29**:287–289.

ABSTRACT

Introduction On 14 March 2020, a state of alarm was declared in Spain because of the pandemic of coronavirus disease (COVID-19). After 12 weeks from the beginning of the pandemic, the number of confirmed cases stoods at 5781 in Aragon: 46% hospitalised, 5% admitted to intensive care unit, and 15% died. The absence of controlled trials in SARS-CoV-2 infection and the fast progression of the disease has promoted the use of treatments with unproven potential benefit. The objective of this study is to define the prescription profile in patients with SARS-CoV-2 infection hospitalised in Aragon, Spain during the pandemic and its adaptation to the official recommendations.

Patients and methods Descriptive retrospective study of the consumption and inpatient dispensation of drugs in a sample of COVID-19 infected inpatients (with positive PCR test result) admitted to hospitals of Aragon, between 1 March and 8 May 2020. Data were collected by an inpatient dispensation software program.

Results 1482 positive COVID-19 patients were analysed: 54.9% male, median age 75 years (IQR 62–85); 12% were admitted to the intensive care unit. Median prescription: 13 active ingredients per patient (IQR 9–19). 73% (1093 patients) received hydroxychloroquine, lopinavir/ritonavir, or azithromycin, 81% as combination therapy. 4.3% (52) received other antivirals. 46% received corticosteroids (84% methylprednisolone, 8.7% dexamethasone) and 2.2% tocilizumab.

Discussion At the time of the study period there was not enough quality evidence to issue a recommendation on any treatment. There are several clinical trials ongoing to clarify what is the best treatment for patient with SARS-CoV-2 infection.

INTRODUCTION

On 14 March 2020, a state of alarm was declared in Spain because of the pandemic of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After 12 weeks from the beginning of the pandemic, the number of confirmed cases stood at 5781 in Aragon, Spain: 46% were hospitalised, 5% were admitted to intensive care unit (ICU), and 15% died. Aragon is one of the autonomous communities in the northeast of Spain, with 1 319 291 inhabitants, and consists of three regions (Huesca, Zaragoza and Teruel).

The progression of the pandemic, with around 700 weekly hospital admissions at the highest rate, respiratory progression in 15% of the cases, and an absence of an effective treatment, resulted in the development of multiple therapeutic combinations, based on the expected aetiopathogenic mechanism of the infection. Most of the prescription recommendations were based on Chinese publications, after that country's experience with ill coronavirus patients, in the absence of controlled clinical trials.

The purpose of this study is to define the prescription profile in patients with SARS-CoV-2 infection hospitalised in Aragon during the pandemic, the most frequent combinations, and the adaption of the prescriptions to the available evidence recommendations provided by societies such us the Infectious Disease Society of America, the American Society of Healh-System Pharmacist, or the National Institutes of Health.

METHODS

This is a descriptive retrospective study of the consumption and inpatient dispensation of drugs in a sample of COVID-19 infected inpatients (with a positive PCR test result) admitted to hospitals in Aragon between 1 March and 8 May 2020, during phases 0–1. These phases refer to the national coronavirus de-escalation plan. It consisted of four steps (phase 0, phase 1, phase 2, and phase 3). Each phase lasted at least 2 weeks before a thorough assessment could determine whether the next phase could be introduced. Phase 0 was the most restrictive phase, followed by phase 1 where limitations were less restrictive.

Data were collected by an inpatient dispensation software program, extracted from the database DATA WORHOUSE. The following data were analysed: age, sex, health sector, active pharmaceutical ingredients (APIs), number of prescribed drugs, and days of treatment. Equivalence was assumed between consumption and dispensation, since the whole study sample was hospitalised. The data collected were analysed with the computer program SPSS V15. Quantitative variables were expressed as median and quartiles or as means and standard deviation, and qualitative variables were expressed in percentages.

RESULTS

A total of 1482 inpatients with confirmed infection were analysed (database can only extract dispensations which were registered in the inpatient dispensation software program: 60% of the patients were hospitalised with COVID-19): 813 (54.9%) of patients were men and 669 (45.1%) were women, with a median age of 75 years (IQR 62–85); 12% were admitted to the ICU. Population distribution according to the province is representative of each health sector (online supplemental table 1).

Table 1 Profile of most frequently prescribed antibiotics, antivirals and inmunomodulatory agents (alone or concurrently with others) during the period of study

Combination therapy	Number of patients	Percentage of patients	N (%) male	N (%) female	Median age (IQR) (years)
Hydroxychloroquine+lopinavir+ritonavir	307	28.09%	191 (62)	116 (38)	68 (57–77)
Hydroxychloroquine+lopinavir/ritonavir+azithromycin	302	27.63%	181 (60)	121(40)	69 (57–77)
Hydroxychloroquine+azithromycin	266	24.34%	130 (49)	136 (51)	75 (61–84)
Azithromycin+lopinavir/ritonavir	7	0.64%	3 (43)	4 (57)	87 (76–91)
Azithromycin	104	9.52%	52 (50)	52 (50)	87 (78–93)
Hydroxychloroquine	88	8.05%	47 (53)	41 (47)	79 (64–83)
Lopinavir/ritonavir	19	1.74%	12 (63)	7 (37)	75 (59–85)
Total	**1093**	**100%**	**616(56)**	**477(44)**	**75(59–80)**

Four hundred and fifty-six APIs were prescribed, at a median per patient of 13 (IQR 9–19) (online supplemental table 2 shows the most frequently prescribed APIs (≥25% of the patients)).

Seventy-three per cent (1093) of the patients received hydroxychloroquine, lopinavir/ritonavir, or azithromycin, 81% as combination therapy (table 1). Mean (SD) treatment duration was 6±3 days with hydroxychloroquine, 5±3 days with lopinavir/ritonavir, and 4±2 days with azithromycin.

Others antivirals were prescribed in 4% of the patients: 27 patients received aciclovir, 13 darunavir/cobicistat, seven oseltamivir, seven tenofovir, three valganciclovir, two valaciclovir, one received remdesivir, one etravirine, and one raltegravir. After ceftriaxone and azithromycin, the antibiotics most frequently prescribed were levofloxacin (13%) and piperacillin/tazobactam (9%); the rest of the antivirals/antibiotics were prescribed in 2–6% of the patients.

Forty-eight per cent (708) of the patients received anti-inflammatory treatment or corticosteroids. Corticosteroids were prescribed in 46% (679) of the patients: 84% received methylprednisolone, 8.7% dexamethasone, 3.8% combined methylprednisolone and dexamethasone, and 3.5% combined corticosteroids and tocilizumab. Mean treatment duration was 5±4 days with dexamethasone and 6.6±5.8 days with methylprednisolone. Other anti-inflamatory drugs prescribed were tocilizumab (2.2%) and sirolimus (0.1%).

Other recommended prescribed treatments were heparin (82%), interferon β (2%), immunoglobulin (0.6%), and interferon α2b (0.1%).

DISCUSSION AND CONCLUSIONS

The characteristics of our study are similar to those reported by other national hospitals during the study period[1]: 46% of the patients were hospitalised (45% in Spain), mainly men (54% Aragon, 57% Spain), with a median age higher than Spain (75 years (IQR 62–85) vs 70 years (IQR 55–81). The sample represents 60% of the COVID-19 hospitalised patients in Aragon.

At this time, there is no effective treatment for COVID-19 infection. Since the beginning of the pandemic, multiple therapeutic approaches have been proposed. Treatment options are antivirals that inhibit enzymatic systems to decrease viral replication and those that inhibit the SARS-CoV-2 cell entry, and immunomodulatory drugs that reduce the cytokine storm and associated lung damage.[2]

Based on the "generated evidence" in clinical practice and data from ongoing studies, the Department of Health issues and updates treatment recommendations for patients with COVID-19 infection.[3] In Aragon, a regional protocol of pharmacological management has been established, underpinned by the best available evidence.

During the first 7 weeks after the pandemic began, the most frequently prescribed drugs for COVID-19 infection were: hydroxychloroquine, azithromycin, and lopinavir/ritonavir, representing 73% (1093) of the patients. Hydroxychloroquine and lopinavir/ritonavir were recommended according to the protocol, alone or in combination. However, the protocol cautioned against the use of hydroxychloroquine and azithromycin in combination due to the absence of beneficial results of concomitant use and the risk of QT prolongation.[4]

Hydroxychloroquine was used in combination in 91% of the patients who received this drug (875/882). The most common association was with lopinavir/ritonavir (35.1%), followed by triple therapy with lopinavir/ritonavir and azithromycin (34.5%), and finally with azithromycin (30.4%). Azithromycin association was present in 64% of the patients with combined prescriptions, 38% (568) of the whole sample. The most frequent prescription of lopinavir/ritonavir was in combination (97%) (table 1).

Combination therapy recommendation is based on the possible synergistic action due to the drugs' different mechanisms of action. However, 12 weeks after the state of alarm was declared, there was no evidence of any benefit. In addition, these drugs may induce cardiac effects, since they increase the risk of QT prolongation. Regarding the use of a combined regimen with azithromycin and hydroxychloroquine, there is very little,[5] contradictory[4] and very low quality evidence, and since they are not free of risk, it is recommended against their use except in a clinical trial (recommendation rating AIII).

Prescription profiles used against the virus are unknown in clinical practice. In a recent systemic review,[6] the most frequently administered drugs were lopinavir/ritonavir (21.9%), followed by hydroxychloroquine (1.2%) and azithromycin (1.4%). These data contrast with our sample study results. Remdesivir was prescribed in only one patient.

The anti-inflammatory treatments proposed to act on disease progression[7] were prescribed in 48% of the patients; the most frequently used were corticosteroids, with a higher degree of immunosuppression (methylprednisolone 84%), similar to other studies.[4] The use of other drugs such as tocilizumab was limited (2.2%). This profile is observed in other studies,[6] with very little use of tocilizumab and higher use of corticosteroids (25%), but still lower than in our sample. Data on the use of corticosteroids are still limited with low quality evidence.[4] It is recommended to not use corticosteroids routinely (recommendation rating AIII),[8] to use them according to the severity of illness, indications and underlying medical conditions, and their use to be considered on a case-by-case basis.[3 4 8 9]

The emergence of the pandemic provided, in its early stages, the basis for the use of these drugs outside of clinical trials. However, despite the recommendations proposed, differences are observed in prescriptions not adapted to the guidelines, not only in our study but also in other publications.

Since this study was based on prescriptions of patients with SARS-CoV-2 infection at the beginning of the pandemic, some options are no longer recommended and used in clinical practice. As treatment recommendations are continually being updated, it would be interesting to see their evolution and compare these results with current lines of treatment.

At the time of the study period, there was not enough quality evidence to issue a recommendation on any treatment, and security alerts have also reported[10] about combination regimens that put patients at risk without any benefit.[10] There are several clinical trials ongoing to clarify what is the best treatment for patients with SARS-CoV-2 infection.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information, de-identified participant data.

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