Study of the effect of Baricitinib on the Course of COVID-19

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Authors’ contributions

This work was carried out in collaboration among all authors. Author AYM did study design, investigation, data curation, wrote and edited the manuscript and search resources; author AAT helped in conceptualization, methodology, writing and editing; author ZAA did study investigation, data analysis; author ATA performed methodology, wrote and edited the manuscript, authors MGMI and MMI did investigation, visualization; author ISB supervised the study; author AEM searched resources; author SNP helped in conceptualization, wrote and edited the manuscript; author OAB reviewed and edited the manuscript. All authors read and approved the final manuscript.

ABSTRACT

The aim of the study was to determine the effect of the inhibitor of janus kinase – baricitinib (“Olumiant”) on the course of COVID-19. This drug baricitinib is able to suppress the systemic inflammatory response, which is one of the common causes of death in COVID-19, is an urgent
problem of the study. The study was carried out in the Regional Specialized Budget Infectious Diseases Hospital of Stavropol (Russian Federation, Stavropol Region). In a multivariate analysis, it was shown that the use of baricitinib was associated with a decrease in the frequency of the primary endpoint of death/need for invasive lung ventilation. The use of baricitinib was quite safe, but in some patients there was an increase in the level of transaminases. No cases of hypercoagulation have been reported while taking baricitinib. It was found that patients with a normal BMI are more sensitive to therapy than those who are overweight. 75% of patients in the first group had a temperature above 38.0°C. However, against the background of taking the standard treatment regimen and baricitinib, it was noted that the temperature stabilized during the day and did not rise again. Against the background of taking baricitinib, the elimination of the phenomena of respiratory failure and the refusal of an oxygen mask occurred 3.1 times more often than without baricitinib. The authors concluded that the use of baricitinib can be considered as an additional therapy for moderate forms of pneumonia in patients over 65 years or in patients with concomitant chronic diseases in order to suppress the reactions of systemic inflammation and the development of serious respiratory and other system lesions caused by COVID-19.

Keywords: COVID-19; Baricitinib; blood analysis.

1. INTRODUCTION

The new severe SARS-CoV-2 pandemic has become a major public health problem, which has included 155 million cases of the disease, 3.2 million of which were fatal [1,2]. The emergence of COVID-19 has given healthcare professionals the task of quickly diagnosing and providing medical care to patients [3-9]. Currently, the intensive study of the clinical and epidemiological features of the disease, the development of new means of its prevention and treatment, continues [2, 10-17].

Most authors are inclined to develop effective antiviral agents. In general, many interesting areas have been covered in recent years. Some scientists suggest using active phytopreparations in food to prevent coronavirus [18-20]. There are works on the study of the venom activity of migalamorphic spiders [21], which concluded that the polypeptide combinations of the studied poisons have strong antiviral activity. The effect of other biologically active substances on antiviral activity has also been studied [22-30]. It is also worth noting the development of digitalization technologies [31-35].

The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy). In 3-4% of patients the development of acute respiratory distress syndrome was registered [36-42]. Some patients develop hypercoagulation syndrome with thrombosis and thromboembolism, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop [43,44].

Thus, in order to suppress hyperinflammation and the development of serious lesions of the lungs and other organs caused by COVID-19, the administration of the tablet drug baricitinib "Olumiant" (Lilly S. A., Avda. Industrial 30, 28108 Alcobendas-Madrid) is used as an additional therapy.

The drug baricitinib is able to suppress the systemic inflammatory response and reduces the risk of cytokine storm, which is one of the common causes of death in COVID-19. This enables us to say that this research problem is relevant.

Objective: to determine the effect of the drug janus kinase inhibitor baricitinib ("Olumiant") on the course of COVID-19 and determine the assessment of the effectiveness of the action and the effect on the body during treatment.

To achieve the objective, the following tasks were solved in the study:

1. Determining the group to study the effect of the drug on the COVID-19;
2. Collection and evaluation of laboratory data during treatment with baricitinib "Olumiant", as well as their comparison with the control group of patients;
3. Evaluation of the effectiveness of the action and the effect on the body during treatment.
2. MATERIALS AND METHODS

The study included 40 patients (2 groups by 20 patients) with a new coronavirus infection caused by COVID-19 aged between 23 to 84 years, with an average age of 61.6 years. The structure of COVID-19 patients was dominated by men-55% (22 people). The average body mass index (BMI) for 40 patients was 23.4. A comparative analysis of laboratory parameters was performed in the group of COVID-19 patients taking baricitinib (n=20) and not taking it (n=20). The patients were examined according to the generally accepted criteria for COVID-19 patients. The analysis was carried out depending on BMI, the presence of insulin resistance, and age [45].

Each group consisted of 20 people. The first group taking baricitinib consisted of 8 men and 12 women, the control group consisted of 15 men and 5 women, respectively (Fig. 1). Among the patients in the experimental group over 65 years old, there were 40%, in the control group – 55% (Fig. 2).

The first group taking baricitinib consisted of 8 men and 12 women, the second (control) group consisted of 15 men and 5 women, respectively. Among the patients in the first group over 65 years old, there were 40%, in the control group – 55%. The number of deaths in the first group is 1/20, in the control group 3/20. At the same time, the number of bed days varies in the average range (18 and 15 days, respectively).

Dosage regimen of baricitinib: 4 mg once a day orally for 7-14 days (according to the Temporary Guidelines of the Ministry of Health of the Russian Federation for the prevention, diagnosis and treatment of new coronavirus infection (COVID-19).

The essence of the main problem of research work determined the need to apply the principles of systematic and complex research, use an integrative approach, study and analyze the state of all the necessary structures and subsystems, and their relationships [46-48].

In this study, the effect of baricitinib on the course of COVID-19 was studied in patients admitted to the State Medical Institution “KSKIB” with radiologically determined COVID-19 pneumonia and laboratory-confirmed infection diagnosed with a positive SARS-CoV-2 RT-PCR (reverse transcription PCR) test using a nasopharyngeal swab. The case histories, laboratory and instrumental studies, and treatment protocols of patients with COVID-19 were analyzed, which included patient demographics, comorbidities, oxygen support, adverse events, concomitant therapy, and clinical outcomes.

This study examined the effect of baricitinib on the course of COVID-19 in patients admitted to the Regional Specialized Budget Infectious Diseases Hospital of Stavropol (Russian Federation, Stavropol Region) with radiologically determined COVID-19 pneumonia.
and laboratory-confirmed infection diagnosed with a positive Sars-CoV-2 test by RT-PCR (reverse transcription PCR) using a nasopharyngeal smear. The case histories, laboratory and instrumental studies, and treatment protocols of patients with COVID-19 were analyzed, which included patient demographics, comorbidities, oxygen support, adverse events, concomitant therapy, and clinical outcomes.

Statistical analysis of obtained data was carried out using Microsoft Excel.

3. RESULTS AND DISCUSSION

Among the patients of the first group, patients with a body mass index (BMI) exceeding the norm (i.e. suffering from some degree of obesity) were 40%, while in the control group only 30%. According to the collected data, it can be seen that patients suffering from overweight had a clear predisposition to diabetes mellitus, and against the background of hormone therapy, they tended to increase the blood glucose index. At the same time, it can be seen that the indicators of various tests of overweight patients of the first group who received baricitinib are much more modest than those who did not suffer from obesity.

Table 1 shows the biochemical analysis of the patient's blood before using baricitinib and after application.

From this, it can be concluded that patients with a normal BMI are more sensitive to therapy than those who are overweight. 75% of patients in the first group had a temperature above 38.0°C. However, against the background of taking the standard treatment regimen and baricitinib, it was noted that the temperature stabilized during the day and did not rise again. More than half of the cases were accompanied by myalgia, which weakened or disappeared completely towards the end of treatment. From the above, it can be concluded that with the correct and timely administration of the drug, the reaction of systemic inflammation is significantly devalued, the temperature decreases, and myalgia is eliminated. In the control group, myalgia remained for a long time, in some patients almost until the time of discharge.

The study involved patients with moderate to severe disease with less than 92% SaO2 (without artificial ventilation of the lungs). All 20 patients of the first group received baricitinib. They were selected for control with a close range of indicators that potentially affect the prognosis. Almost half of the patients included are over the age of 65, as mentioned in Fig. 2. Most of the patients also received hydroxychloroquine and ingavirin, antibiotics, and glucocorticosteroids. In a multivariate analysis, it was shown that the use of baricitinib was associated with a decrease in the frequency of the primary endpoint of death/need for artificial ventilation. The use of
baricitinib was quite safe, but in some patients, there was an increase in the level of transaminases. No cases of hypercoagulation were reported while taking baricitinib.

Against the background of taking baricitinib, the elimination of the phenomena of respiratory failure and the refusal of an oxygen mask occurred 3.1 times more often than without baricitinib.

Phenomena from the gastrointestinal tract consisted the appearance of flatulence and constipation. In the group taking baricitinib, the phenomenon was almost 4 times more common than in the control group. But those patients who took hydroxychlorine in combination with (or without) baricitinib had a tendency to profuse diarrhea.

The results of blood tests of patients of the experimental and control groups are presented in Tables 2-4.

According to the results presented in Tables 2-4, baricitinib had the most favorable effect in patients with moderate to severe degrees of the course of acute coronavirus infection. But patients with normal BMI values were more sensitive to the drug. The use of baricitinib can be considered as an additional therapy for moderate forms of pneumonia in patients over 65 years or in patients with concomitant chronic diseases in order to suppress the

### Table 1. Influence of baricitinib on blood parameters

| Index                        | Results Before baricitinib application | Reference values |
|------------------------------|----------------------------------------|------------------|
|                              |                                       |                  |
| Cholesterol                  | 4.8                                    | 3.1-5.2          |
| Triglycerides                | 1.2                                    | <1.7             |
| High-density lipoproteins    | 1.6                                    | 1.04-1.55        |
| Low-density lipoproteins     | 2.4                                    | < 3.4            |
| Glucose                      | 5.5                                    | 3.3-5.6          |
| Atherogenic index            | 1.8                                    | 0-3              |

### Table 2. Visual indicators of changes in some parameters of the general blood test in patients taking baricitinib

| HGB (g/l) initial | HGB (g/l) final | HCT (%) initial | HCT (%) final | RBC \(*10^{12}/l\) | RBC \(*10^{12}/l\) | WBC \(*10^9/l\) initial | WBC \(*10^9/l\) final |
|------------------|----------------|----------------|---------------|-------------------|-------------------|------------------------|-----------------------|
| 155              | 126            | 44.4           | 34.6          | 5.63              | 4.55              | 9.8                    | 14.7                  |
| 157              | 154            | 44.7           | 41            | 5.53              | 5.01              | 10.9                   | 15.9                  |
| 135              | 136            | 40.7           | 38.3          | 4.55              | 4.5               | 7                      | 7.1                   |
| 149              | 154            | 42.4           | 43.4          | 4.72              | 5.01              | 1.4                    | 8.4                   |
| 118              | 127            | 33.4           | 34.8          | 3.85              | 4.19              | 8.1                    | 6.5                   |
| 133              | 119            | 39.2           | 35.7          | 4.57              | 4.06              | 4.4                    | 5.6                   |
| 158              | 160            | 44.3           | 43.5          | 5.09              | 5.09              | 9.7                    | 6.6                   |
| 119              | 120            | 32.4           | 33.4          | 4.19              | 4.24              | 5.9                    | 4.49                  |
| 136              | 124            | 39.9           | 35.7          | 4.65              | 4.29              | 13.3                   | 5.6                   |
| 93               | 93             | 39.9           | 38.6          | 4.55              | 4.46              | 3.9                    | 8.5                   |
| 89               | 90             | 40             | 39.1          | 4.8               | 4.3               | 4                      | 8                     |
| 139              | 205            | 29.9           | 62.4          | 4.43              | 6.73              | 22.6                   | 6.5                   |
| 165              | 145            | 47.9           | 39.7          | 5.46              | 4.78              | 7                      | 10.1                  |
| 118              | 146            | 34.1           | 43.5          | 3.61              | 4.68              | 5.1                    | 12                    |
| 120              | 102            | 29.9           | 62.1          | 4.13              | 3.6               | 2.9                    | 4.4                   |
| 116              | 122            | 44.4           | 43.5          | 4                 | 4.21              | 7.2                    | 9.2                   |
| 144              | 143            | 29.9           | 62.3          | 4.67              | 4.61              | 4.6                    | 7.3                   |
| 140              | 128            | 29.3           | ymep          | 4.84              | 4.46              | 3.3                    | 9.3                   |
| 120              | 147            | 32.4           | 33.4          | 4.19              | 4.24              | 5.9                    | 4.49                  |
Table 3. Visual indicators of changes in some parameters of the biochemical blood test in patients taking baricitinib

| Albumin g/l | ALT l max | AST l max | AST/ALT | Lactate Dehydrogenase l-1 max | Creatine phosphokinase l-1 max | Creatinin µmol/l initial | Creatinin µmol/l final |
|------------|-----------|-----------|---------|-------------------------------|------------------------------|------------------------|-----------------------|
| 44.2       | 78        | 101       | 1.29    | 994.5                        | 49.49                        | 83                     | 67                    |
| 30.2       | 200       | 134.4     | 0.67    | 706.8                        | 946                          | 90                     | 83                    |
| 39.5       | 150.3     | 65        | 0.43    | 1005.9                       | 96.12                        | 79                     | 61                    |
| 31.2       | 150.3     | 65        | 0.43    | 1021                         | 30.81                        | 81                     | 72                    |
| 43.5       | 92.7      | 42.1      | 0.45    | 342                          | 21.62                        | 69                     | 75                    |
| 39.2       | 78.8      | 27.6      | 0.35    | 547                          | 18.4                         | 96                     | 69                    |
| 42.1       | 106.7     | 75.1      | 0.70    | 28.48                        | 28.48                        | 73                     | 81                    |
| 31.1       | 24        | 32.3      | 1.34    | 359.6                        | 15.75                        | 75                     | 60                    |
| 43.2       | 79.4      | 72.9      | 0.91    | 250.5                        | 15.9                         | 65                     | 69                    |
| 44         | 37.2      | 36.6      | 0.80    | 353.66                       | 18.32                        | 62                     | 59                    |
| 49         | 37.2      | 36.5      | 0.80    | 353.66                       | 18.32                        | 62                     | 59                    |
| 28         | 193       | 140       | 0.72    | 342.6                        | 57.9                         | 88                     | 75                    |
| 30.5       | 29        | 43.6      | 1.50    | 334.3                        | 215.4                        | 83                     | 90                    |
| 29         | 25.3      | 20.3      | 0.80    | 325                          | 18.95                        | 160                    | 190                   |
| 46.2       | 29.2      | 44.8      | 1.53    | 526.5                        | 320.9                        | 138                    | 96                    |
| 38.5       | 99.5      | 43.2      | 0.43    | 1194.2                       | 24.1                         | 31                     | 78                    |
| 41.2       | 33.6      | 36.9      | 1.34    | 518.2                        | 50.47                        | 112                    | 88                    |
| 31.1       | 26.6      | 36        | 1.35    | 223.9                        | 78.4                         | 92                     | 79                    |
| 31.1       | 24        | 32.3      | 1.34    | 359.6                        | 15.75                        | 75                     | 60                    |

Table 4. Visual indicators of changes in some parameters of the blood coagulogram in patients taking baricitinib

| Prothrombin index % initial | Prothrombin index % final | APTT* initial | APTT final | fibrinogen g/l initial | fibrinogen g/l final |
|-----------------------------|---------------------------|---------------|------------|------------------------|----------------------|
| 80                          | 84                        | 30            | 37         | 3.34                   | 2.6                  |
| 86                          | 74                        | 29            | 32         | 2.63                   | 2.89                 |
| 89                          | 90                        | 45            | 25         | 2.59                   | 2.86                 |
| 88                          | 78                        | 32            | 36         | 2.83                   | 2.55                 |
| 81                          | 77                        | 30            | 20         | 2.57                   | 2.33                 |
| 90                          | 91                        | 51            | 35         | 3.55                   | 3.17                 |
| 98                          | 97                        | 30            | 36         | 4.59                   | 3.24                 |
| 85                          | 86                        | 24            | 20         | 3.38                   | 3.35                 |
| 93                          | 90                        | 29            | 28         | 3.21                   | 3.6                  |
| 86                          | 78                        | 24            | 22         | 3.28                   | 3.8                  |
| 85                          | 79                        | 49            | 40         | 2.6                    | 2.7                  |
| 69                          | 79                        | 40            | 36         | 2.73                   | 2.64                 |
| 89                          | 89                        | 29            | 25         | 3.92                   | 3.79                 |
| 80                          | 84                        | 28            | 33         | 3.39                   | 3.39                 |
| 92                          | 90                        | 30            | 32         | 4.42                   | 4.4                  |
| 88                          | 87                        | 29            | 24         | 3.85                   | 3.76                 |
| 105                         | 82                        | 23            | 33         | 4.44                   | 3.34                 |
| 92                          | 94                        | 25            | 21         | 3.78                   | 4.38                 |
| 85                          | 86                        | 24            | 20         | 3.38                   | 3.35                 |

*Activated partial thromboplastintime

reactions of systemic inflammation and the development of serious respiratory and other system lesions caused by COVID-19. Against the background of taking the standard treatment regimen and baricitinib, it was noted that the temperature stabilized during the day and did not rise any more. More than half of the cases were accompanied by myalgia, which weakened or disappeared completely towards the end of the treatment. It can be concluded that with the correct and timely administration of the drug, the reaction of systemic inflammation is significantly
devalued (can be traced by the values of CRP), the temperature decreases and myalgia is eliminated. It should hence be concluded that the drug baricitinib against rheumatoid arthritis has significant prospects for the treatment of COVID-19 in moderate to severe patients. This is especially true for men over 65 years of age. For younger patients, a separate study should be performed. But taking baricitinib reduces the risk of hypercoagulation, clearly indicates that the risk of vascular accidents is reduced, both in younger and older patients. Despite the positive dynamics in the tests against the background of taking the drug, further trials and studies are needed, especially in groups of patients with various comorbid pathologies.

In a multivariate analysis, it was shown that the use of baricitinib was associated with a decrease in the frequency of the primary endpoint of death/need for invasive lung ventilation. The use of baricitinib was quite safe, but in some patients there was an increase in the level of transaminases. No cases of hypercoagulation have been reported while taking baricitinib.

4. CONCLUSION

Routine use of baricitinib in patients with COVID-19 cannot be recommended until clinical efficacy and safety studies are available. But the results of recent studies (including the current one) are more than positive; the study of the effect of this drug is promising and necessary.

In a multivariate analysis, it was shown that the use of baricitinib was associated with a decrease in the frequency of the primary endpoint of death/need for invasive lung ventilation. The use of baricitinib was quite safe, but in some patients there was an increase in the level of transaminases. No cases of hypercoagulation have been reported while taking baricitinib. It was found that patients with a normal BMI are more sensitive to therapy than those who are overweight. 75% of patients in the first group had a temperature above 38.0°C. However, against the background of taking the standard treatment regimen and baricitinib, it was noted that the temperature stabilized during the day and did not rise again. Against the background of taking baricitinib, the elimination of the phenomena of respiratory failure and the refusal of an oxygen mask occurred 3.1 times more often than without baricitinib. The use of baricitinib can be considered as an additional therapy for moderate forms of pneumonia in patients over 65 years or in patients with concomitant chronic diseases in order to suppress the reactions of systemic inflammation and the development of serious respiratory and other system lesions caused by COVID-19.

Applicable dosage of baricitinib: 4 mg once a day orally for 7-14 days (according to the Temporary Guidelines of the Ministry of Health of the Russian Federation for the prevention, diagnosis and treatment of new coronavirus infection (COVID-19, version 6 of 08.04.2020).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL AND CONSENT

The work was approved by the ethics committee of the Regional Specialized Budget Infectious Diseases Hospital of Stavropol. All patients signed consent to participate in the experiment in accordance with the standard form used in the Regional Specialized Budget Infectious Diseases Hospital of Stavropol. Blood sampling and examination were performed according to the procedure described in [32,43].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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