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Real-Life Advantages and Limits of Baricitinib for the Late Treatment of Adults Hospitalized with COVID-19

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Abstract: Baricitinib, a reversible Janus-associated kinase-inhibitor, is approved for treating COVID-19, combined with Dexamethasone and, eventually, with Remdesivir (RDV). This retrospective cohort study assesses the real-life advantages and limits of Baricitinib in the current pandemic scenario. Data of all patients consecutively hospitalized with moderate/severe COVID-19 between 1 October 2021 and 31 March 2022 were retrospectively collected and described according to the treatment received (Baricitinib, Baricitinib + RDV, none). We performed survival analyses to estimate the 21-day probability of Intensive Care Unit (ICU) admission, death, and composite. We built multivariate Cox regression models to identify ICU admission/death predictors among patients' features. Of 111 subjects, 28 received Baricitinib, 21 received Baricitinib + RDV, and 62 could not be treated due to pre-existing conditions. Treated patients had a comparable risk of death (HR 0.50, 95% C.I. 0.20–1.26, $p = 0.14$) but remarkably lower risk of 21-day ICU admission (H.R., 0.10, 95% C.I., 0.01–0.86, $p = 0.03$), regardless of the type of treatment received. At multivariable analysis, older age was the only predictor of ICU admission/death (HR 1.14, 95% C.I. 1.03–1.26, $p \leq 0.01$).Although effective, the high prevalence of elderly, co-morbid patients limits Baricitinib use in the current pandemic setting.

Keywords: COVID-19; Baricitinib; real-life study

Citation: Poliseno, M.; Lacedonia, D.; Niglio, M.; De Gregorio, F.; Minafra, G.A.; Campanino, T.; Giganti, G.; Scioscia, G.; Santantonio, T.A.; Foschino Barbaro, M.P.; et al. Real-Life Advantages and Limits of Baricitinib for the Late Treatment of Adults Hospitalized with COVID-19. *BioMed* **2023**, *3*, 236–245. https://doi.org/10.3390/biomed3020021

Academic Editor: Wolfgang Graier

Received: 7 April 2023
Revised: 27 April 2023
Accepted: 4 May 2023
Published: 8 May 2023

1. Introduction

According to case notification rates, due to the relentless spread of Omicron sub-lineages, the number of new SARS-CoV-2 infections in Europe and Italy has constantly risen since the last months of the year 2021. Moreover, albeit a decrease in the death rate has been reported in almost all countries individually, some severity indicators—above all, hospitalization rates—are increasing [1]. The high vaccination coverage has gradually changed the features of subjects at risk of developing moderate to severe forms of COVID-19 who are now mainly individuals with low immunogenic response to COVID-19 vaccines such as immunocompromised (especially patients with cancer, solid organ transplant, end-stage renal disease, and rheumatic immune-mediated diseases on immunosuppressive treatment) and elderly (aged 65 and above) populations [2].

For these patients, the probability of being hospitalized with SARS-CoV-2 pneumonia with oxygen requirement or developing severe COVID-19 disease with acute respiratory failure after hospital admission due to other causes is not negligible [3].

National Institute of Health (NIH) Guidelines recommend the use of Baricitinib, a reversible Janus-associated kinase inhibitor, for the treatment of patients hospitalized

with COVID-19 in the presence of systemic inflammatory syndrome and rapidly increasing oxygen needs, in combination with Dexamethasone and, possibly, with Remdesivir [4].Evidence from randomized clinical trials (RCTs) has demonstrated that when administered with the standard of care (including Dexamethasone), treatment with Baricitinib was associated with reduced mortality in hospitalized adults with COVID-19, especially among those receiving high-flow oxygen or non-invasive ventilation. In particular, it was observed that Baricitinib, when associated with Remdesivir, was superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status [5,6]. Moreover, the drug has other favorable features, such as a short half-life, limited drug-drug interactions, flexible dosing, oral administration, short dose duration, and a safety profile similar to the standard of care alone [7].

Nevertheless, some clinical questions remain unanswered regarding using Baricitinib (as well as other immune-modulating treatments) in the advanced stages of COVID-19.

Among them, the risk of slow viral clearance, the enhanced susceptibility to secondary opportunistic infections and possible bacterial/fungal superinfections, and a possible worsening of kidney function in subjects presenting with chronic and acute-on-chronic kidney failure [7,8].

These conditions are recently acquiring growing importance in real-world clinical practice due to some typical features of patients hospitalized in the current pandemic setting (age, co-morbidities, pre-existing immune depression).

Data regarding using Baricitinib in real-life could eventually support the clinician during a daily risk-benefit assessment, but evidence from the scientific literature is still scarce.

This study aims to outline the applicability of immune-modulating treatment with Baricitinib in a real-life cohort of patients hospitalized with SARS-CoV-2 pneumonia and oxygen requirement and highlight the possible limitations connected to its use that could not have adequately emerged from RCTs.

As a secondary aim, we will analyze the study population's clinical outcomes to understand if the advantages of prescribing a specific medical treatment (Baricitinib, alone or in combination with Remdesivir), stated by the Guidelines, could also be obtained in real-life setting.

2. Materials and Methods

2.1. Study Design

The longitudinal, retrospective, observational clinical cohort study was performed in the Respiratory Diseases and Infectious Diseases Unit of Foggia University Hospital from 1 October 2021 to 31 March 2022.

Features of all patients with moderate to severe SARS-CoV-2 pneumonia and oxygen requirement who were consecutively hospitalized in the study period were retrospectively collected.

After baseline evaluation, intravenous Remdesivir (RDV) 100 mg Q.D. after loading dose was administered in patients who required low-flow oxygen at hospital admission and were hospitalized within 10 days from symptom onset. Oral treatment with Baricitinib for 10 days was consecutively started in patients with rapidly evolving COVID-19 pneumonia who required High Flow Nasal Cannula (HFNC) or Non-Invasive Ventilation (NIV) within the first 24 h after admission. Once started, treatment with Remdesivir was continued for up to 5 days, even if patients' respiratory conditions worsened.

When not contraindicated, individuals with acute respiratory failure requiring HFNC or NIV at hospital admission were only prescribed 10 days of oral Baricitinib without Remdesivir.

Baricitinib was prescribed at 4 mg Q.D. or 2 mg in case of impaired renal function. Given the immune-suppressive mechanism of action of the drug that could significantly reduce the host immune response and increase the viral replication if administered close to

symptoms onset, treatment was administered only in those subjects reporting COVID-19 symptoms for at least seven days.

Low-Molecular-Weight Heparin and Dexamethasone were also administered according to NIH guidelines [4].

We avoided the Baricitinib prescription:

in patients who reported COVID-19 symptom onset <7 days;
in patients with Chronic Kidney Disease (CKD) with an estimated Glomerular Filtration rate below 15 mL/min;
in subjects who tested positive at anti-HBV screening performed at baseline;
in those presenting with suspected or confirmed bacterial co-infections (Procalcitonin above five ng/mL).

Once started, treatment with Baricitinib was continued even after ICU transfer, up to a total of 10 days duration.

2.2. Data Collection and Statistical Analysis

Data regarding sex, age, vaccinal status, smoking habits, significant co-morbidities, CCI score, duration of COVID-19 symptoms, laboratory test and Oxygen requirement at admission, type of treatment received (Baricitinib, Baricitinib + Remdesivir, none), duration of hospitalization, and clinical outcomes were retrospectively collected from medical charts. Descriptive statistics were performed for each treatment group and untreated patients and reported in terms of number and percentages for categorical variables and mean (±Standard Deviation, SD) or median (Inter Quartile Range, IQR) for continuous variables, following their parametric or non-parametric distribution. The Chi-square test/Fisher exact test and non-parametric ANOVA were used, as appropriate, to test the null hypothesis of no differences between groups. Kaplan–Meier curves were built to estimate the 21-day probability of ICU admission, death, and the composite among study participants. The Cox univariate and multivariate regression corrected for sex, age, vaccinal status, mean CCI, the mean time interval from symptom onset to hospitalization, presence of Diabetes, CKD, chronic neurologic diseases, and, lastly, type of treatment received (Baricitinib with or without Remdesivir) were performed to identify factors associated with ICU admission/death in the overall study population. A $p < 0.05$ was considered statistically significant. Analysis was performed using Jamovi 2.3.2.

3. Results

A total of 111 subjects, 70% males, median (IQR) age of 70 (61–82) years, were enrolled. The main clinical and socio-demographic features are reported in Table 1.

Baricitinib was administered to 49 patients. Additionally, 21 also received Remdesivir (RDV), and 62/111 (55%) patients did not receive any treatment. Notably, older age (median 77 IQR 70–86 years, $p = 0.005$), higher baseline white blood cell (WBC) count (mean 9.5×10^3 cells/mm^3 (SD 4.8, $p = 0.002$), higher Charlson Co-morbidity Index (CCI) (mean $5 \pm$ SD 2, $p = 0.01$) with higher prevalence of Chronic Kidney Disease (CKD) (14 patients, 13%, $p = 0.02$) and chronic neurologic diseases (14 patients, 13%, $p = 0.05$) were observed in this subgroup. Of 111 patients, 58 (52%) were vaccinated, 26 of whom (23%) had a vaccine and received a booster dose. No significant difference was observed between treated and untreated patients about the proportion of vaccinated individuals.

After a median of 18 (12–23) days of hospital stay, 81 patients (73%) were discharged. Throughout hospitalization, 9 subjects (8%) were transferred to the Intensive Care Unit (ICU), and 21 (19%) died (incidence rate of 29 × 100 patients-months Follow-Up).

Table 1. General features of the study population.

Variables	Total (N = 111)	Untreated (N = 62)	Baricitinib (N = 28)	Baricitinib + RDV (N = 21)	*p*-Value
Male gender, n (%)	70 (53)	31 (50)	23 (82)	16 (76)	**0.005** ^
Age (median, IQR)	73 (61–82)	77 (70–86)	66 (59–80)	68 (56–73)	**0.005** §
Vaccinate *, n (%)	58 (52)	34 (54)	12 (42)	12 (57)	0.51 ^
Vaccinate with booster dose, n (%)	26 (23)	17 (26)	7 (25)	2 (9)	0.24 ^^
Co-existing conditions, n (%)					
Chronic Heart Disease	70 (63)	43 (69)	16 (57)	11 (52)	0.23 ^
Type II Diabetes	31 (31)	20 (32)	8 (28)	6 (28)	0.89 ^
Chronic Kidney Disease	16 (14)	14 (22)	1 (3)	1 (5)	**0.02** ^^
Chronic Obstructive Pulmonary Disease	24 (22)	12 (19)	7 (25)	5 (23)	0.83 ^
Asthma	3 (2)	2 (3)	0 (0)	1 (3)	0.24 ^^
Dementia	20 (18)	13 (20)	4 (14)	3 (14)	0.64 ^^
Chronic neurological diseases	19 (17)	14 (22)	5 (17)	0 (0)	**0.05** ^^
Cancer	14 (13)	10 (16)	3 (11)	1 (3)	0.36 ^^
Primitive Immunodepression	7 (6)	4 (6)	1 (3)	2 (9)	0.69 ^^
Acquired Immune depression	12 (11)	6 (9)	3 (10)	3 (14)	0.85 ^^
Charlson Co-morbidity Index, mean (±SD)	4 (2)	5 (5)	4 (14)	3 (14)	**0.01** §
Smoker, n (%)	39 (40)	20(32)	8 (28)	1 (3)	**0.01** ^^
Laboratory test at admission					
WBC, cells × 10^3/mm^3 **	8.1 (4.5)	9.5 (4.8)	7.3 (4.1)	5.9 (3.1)	**0.002** §
Lymphocytes, cells × 10^3/mm^3 ***	774 (423–1070)	689 (96–1192)	742 (443–850)	915 (678–11,423)	0.13 §
HB, gr/dL **	13 (3)	12 (2)	14 (2)	13 (2)	**0.07** §
PLT, cells × 10^3/mm^3 **	238 (93)	243 (106)	245 (81)	217 (74)	0.40 §
D-Dimers, ng/mL ***	1111 (722–1888)	1351(972–2141)	961 (709–1980)	1063 (660–1752)	0.35 §
Fibrinogen, gr/dL **	604 (339)	587 (262)	631 (259)	592 (186)	0.79 §
IL-6, pg/mL ***	17 (8–37)	17 (9–38)	16 (10–36)	17 (8–34)	0.96 §
CRP, mg/L ***	64 (26–117)	48 (16–146)	77 (37–109)	54 (29–99)	0.52 §
Oxygen requirement during hospitalization, n (%)					
Venturi Mask/Nasal Cannulas	40 (36)	34 (54)	4 (14)	2 (9)	
High Flow Nasal Cannulas	12 (11)	2 (3)	5 (17)	5 (23)	**<0.001** ^^
Non-Invasive Ventilation	59 (53)	26 (41)	19 (67)	14 (66)	
Outcome, n (%)					
Discharged	81 (73)	40 (64)	22 (78)	19 (90)	
Intensive Care Unit admission	9 (8)	8 (12)	1 (3)	0 (0)	
Dead	21 (19)	14 (22)	5 (17)	2 (9)	0.12 ^^
Hospitalization from symptoms onset, median (IQR)	6 (1–10)	3 (1–9)	7 (5–11)	8 (5–10)	0.06 §
Duration of Hospital Stay, days, median (IQR)	18 (12–23)	14 (9–20)	21 (18–25)	20 (15–25)	**<0.001** §

RDV: Remdesivir; HB: Haemoglobin; PLT: Platelets; IL-6: Interleukin-6; RPC: C Reactive Protein; SD: Standard Deviation; IQR: Interquartile Range; * with at least 2 vaccine doses; ** mean (±SD); *** median (IQR); ^ Chi-square test; ^^ Fisher exact test; § Non-parametric ANOVA (Kruskal Wallis test).

At survival analyses, patients receiving any treatment had a significantly lower 21-day probability of ICU admission when compared to untreated subjects (Hazard Ratio, H.R., 0.10, 95% Confidence Interval, C.I., 0.01–0.86, Log-rank $p = 0.03$, Figure 1), although the 21-day risk of death did not significantly differ between the two groups (HR 0.50, 95% C.I. 0.20–1.26, Log-rank $p = 0.14$).

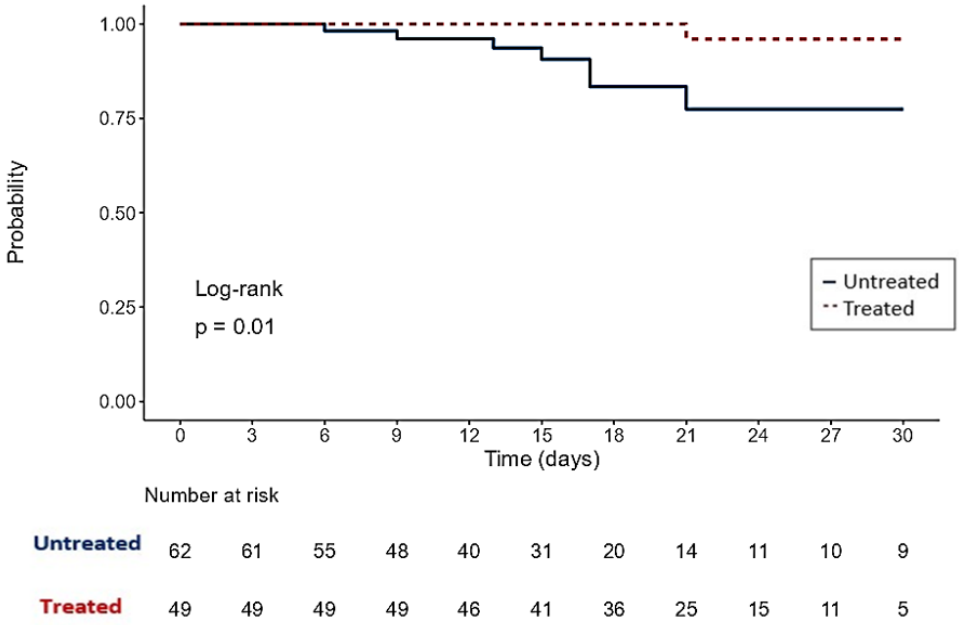

Figure 1. Kaplan–Meier estimates for the 21-day probability of ICU admission in those who received standard care plus Baricitinib, alone or in combination with Remdesivir (Treated group). Compared to the Untreated group, a lower risk (HR 0.10, 95% C.I. 0.01–0.86, Log-rank $p = 0.03$) was reported among treated patients.

A lower 21-day risk (HR 0.39, 95% C.I. 0.15–1.01, $p = 0.04$)was also reported for the composite outcome of ICU admission or death (Figure 2).

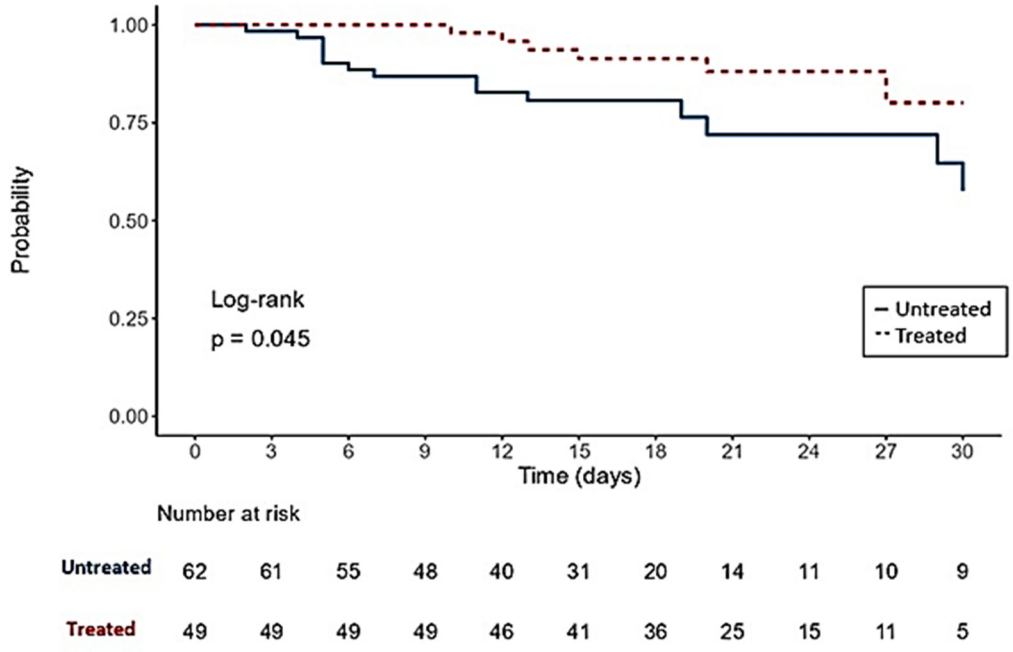

Figure 2. Kaplan–Meier estimates for the 21-day probability of ICU admission/death in treated patients. Compared to the Untreated group, a lower risk (hazard ratio (H.R.) 0.39, 95% C.I. 0.15–1.01, $p = 0.04$) of bad outcomes was noticed among treated patients.

Finally, no significant difference (HR 0.74, 95% C.I. 0.14–4.05, $p = 0.73$) was observed for the composite outcome of ICU admission or death based on the type of treatment received (Figure 3).

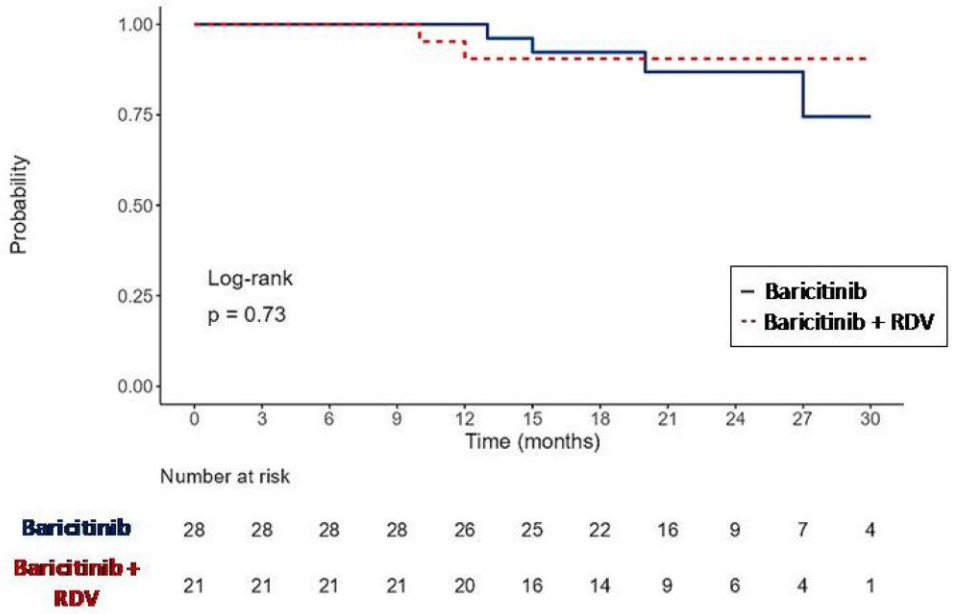

Figure 3. Kaplan–Meier estimates for the 21-day probability of ICU admission/death in patients treated with Baricitinib alone vs. patients treated with Baricitinib and Remdesivir (RDV). No significant difference (HR 0.74, 95% C.I. 0.14–4.05, $p = 0.73$) was observed based on the type of treatment received.

At univariable Cox regression analysis, older age (HR 1.11, 95%C.I. 1.06–1.17, $p < 0.001$), presence of neurologic diseases (HR 5.15, 95% C.I. 2.13–12.44, $p < 0.001$), and higher CCI (HR 1.62, 95% C.I. 1.26–2.09, $p < 0.001$) were predictors of worse outcome, among whom only age (HR 1.13, 95% C.I. 1.01–1.26, $p = 0.03$) resulted as statistically significant at the multivariable model (Table 2). Surprisingly, receiving at least two vaccine doses resulted in noninfluential in preventing COVID-19 progression in our cohort.

Table 2. Cox Univariate ad Multivariate regression analysis assessing predictors of 21-day ICU admission/death risk among study participants.

Variables	H.R. (95% C.I., *p*-Value)	aHR (95% C.I., *p*-Value)
Male sex	0.68 (0.28–1.66, $p = 0.39$)	1.10 (0.38–3.17, $p = 0.86$)
Age (×1-year increase)	**1.11 (1.06–1.17, $p < 0.001$)**	**1.13 (1.01–1.26, $p = 0.03$)**
Vaccinate *	2.15 (0.83–5.61, $p = 0.12$)	1.13 (0.36–3.52, $p = 0.83$)
Type II Diabetes	0.43 (0.13–1.47, $p = 0.177$)	1.04 (0.20–5.35, $p = 0.96$)
Chronic Kidney Disease	2.20 (0.80–6.06, $p = 0.13$)	2.26 (0.49–10.39, $p = 0.29$)
Chronic Neurological Disease	**5.15 (2.13–12.44, $p < 0.001$)**	3.39 (0.91–12.62, $p = 0.07$)
Treatment with Baricitinib	0.42 (0.16–1.09, $p = 0.07$)	0.52 (0.13–2.03, $p = 0.35$)
Treatment with Baricitinibandand Remdesivir	0.43 (0.10–1.88, $p = 0.26$)	1.54 (0.20–11.68, $p = 0.67$)
Non-Invasive Ventilation requirement	2.14 (0.77–5.94, $p = 0.14$)	2.36 (0.72–7.72, $p = 0.15$)
Charlson Co-morbidity Index	**1.62 (1.26–2.09, $p < 0.001$)**	0.77 (0.40–1.51, $p = 0.45$)
Days from symptom onset to hospitalization (×1-day increase)	1.00 (0.93–1.07, $p = 0.91$)	1.05 (0.97–1.13, $p = 0.23$)

* with at least 2 vaccine doses.

4. Discussion

The spectrum of clinical manifestations of COVID-19 is hugely varied, ranging from asymptomatic infections to cases of moderate to critical severity [9,10].

It is known that an over-exuberant immune response could relate to a sudden and rapid clinical deterioration manifesting as acute respiratory distress syndrome and multiorgan failure around days 7–10 of hospitalization when viral titers start to decline [11,12].

This theory has led to repurposing, for the treatment of COVID-19, immune-modulating drugs that inhibit one or more components of the proinflammatory cascade, with the hope that blocking this process may result in improved clinical outcomes. This is the case for Baricitinib, a small molecule reversible inhibitor of Janus-associated kinase, which was already available in over 65 countries for treating adults with moderate to severe rheumatoid arthritis [7].

It was demonstrated that patients with COVID-19 treated with Baricitinib had marked reduced serum levels of IL-6, IL-1β, and TNF-α, rapid recovery of circulating T and B cell frequencies, and increased antibody production against the SARS-CoV-2 spike protein [13]. This modulation of the patient's immune landscape clinically translates to a safer, more favorable clinical outcome for patients with COVID-19 pneumonia, observed in the major clinical trials. In particular, in the COV-BARRIER trial, Baricitinib, in addition to the standard of care, showed a similar safety profile to that of the standard of care alone and was associated with a reduced 28 days-mortality-rate for any cause in hospitalized adults with COVID-19 with non-invasive ventilation requirement [5].

Surprisingly, the same result was observed in an exploratory trial on critically ill hospitalized patients with COVID-19 who were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation. However, these observations still need phase-3 trial confirmation [14]. Khalil et al. also demonstrated that when associated with Remdesivir, the use of Baricitinib reduces the mean time to recovery and a more significant improvement in clinical status at day 15 [6]. Similar encouraging results were observed in a few real-world experiences [15] in which Baricitinib was found to reduce intensive care unit admissions of COVID-19 pneumonia and to decrease the SARS-CoV-2 viral burden detected by nasopharyngeal swabs.

The need for an effective treatment for severe forms of COVID-19 is more of the day than ever, despite the successful vaccination campaign performed all over Europe. Still, a remarkable proportion of elderly and fragile patients remains at high risk of SARS-CoV-2 infection, disease progression, and, ultimately, hospitalization, possibly leading to ICU admission and death.

This phenomenon was observed in our cohort, where patients were mainly vaccinated but presented with median age exceeding 70 years and a mortality rate of almost 20%. In light of these considerations, a 10- to 14-days course of oral 4 mg Baricitinibaadministered not earlier than 7 to 10 days after symptoms onset seems a convenient and cost-saving treatment option for patients hospitalized with COVID-19 with rapidly increasing oxygen needs, with relevant efficacy in reducing the risk of poor outcomes.

Nonetheless, some practical issues arise from the well-known aspects of the drug's mechanism of action and its safety profile and deserve more profound investigation.

It is known that the JAK-STAT signaling pathway (mainly mediated by the Janus kinases 1 and 2), activated by interferons, is the basis of the up-regulation of interferon-controlled genes, whose transcriptional products contribute to rapidly killing the virus-infected cells [16,17]. Consequently, JAK-STAT signal blocking by Baricitinib, impairing interferon-mediated antiviral response, could potentially facilitate the evolution of SARS-CoV-2 infection and increase the risk of delayed viral clearance, which deserves a careful evaluation in terms of timing of administration since reported COVID-19 symptoms onset [7,18].

In our experience, hospital admission was overall referred after a median of 6 days from symptom onset and significantly before among patients who did not receive any treatment. In most cases, dating back to the onset of the symptoms was unease, thus further complicating the clinical decision-making process. The recalled mechanism of action is also a reasonable cause of enhanced vulnerability to secondary opportunistic infections, such as reactivation of herpes zoster and simplex infection, as observed in rheumatologic

patients using Baricitinib and other selective JAK-1 kinase inhibitors (Upadacitinib and Filgotinib) [8,19,20].

For similar biochemical reasons, an improper administration of immune-modulating treatment could worsen underlying septic conditions. Unfortunately, the latter is among the leading causes of hospital admission among elderly patients [21] and is counted as the most frequent healthcare-associated complication in the course of COVID-19 [22,23]; to note, patients who did not receive any treatment in our cohort reported remarkably higher mean WBC count at admission, compared to other groups.

The impact of age on COVID-19 is two-folded: on the one hand, older age has been recognized as an independent predictor of poor COVID-19 outcomes; on the other, SARS-CoV-2 infection often has a detrimental effect on co-existing co-morbidities, which are more frequent among older patients [24,25].

About this point, we wish to underline that in our experience, the clinicians often chose to avoid Baricitinib prescription due to the high prevalence of chronic and acute-on-chronic kidney failure, patients' inability to swallow tablets, and, lastly, episodes of rapid and fatal COVID-19 progression, all conditions which are extremely frequent among older subjects.

Our study has some limitations:

First of all, its retrospective nature, which sometimes prevented us from collecting some information, such as the kind and severity of reported adverse events, the possible onset of bacterial/fungal super-infection, and any laboratory tests performed after treatment with Baricitinib which could be data of great interest for future analysis regarding the drug toxicity. At the same time, we could not trace patients' journeys after ICU admission, possibly underestimating the death rate in our cohort.

Moreover, for what concerns the efficacy of the association of Baricitinib with Remdesivir, our findings are apparently in contrast with the existing literature, which shows the superiority of the association of Baricitinib plus Remdesivir and possibly Dexamethasone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, especially among those receiving high-flow oxygen or non-invasive ventilation [6,15]. In light of this evidence, this treatment strategy is recommended by International Guidelines to be used in similar clinical contexts [4]. Unfortunately, we could not demonstrate a better efficacy of the association of Baricitinib + Remdesivir vs. Baricitinib alone, even though a slightly lower hazard ratio of ICU admission/death was reported (HR 0.74, 95% C.I. 0.14–4.05, $p = 0.73$). Given the wide Confidence Interval, the small number of patients in the two groups could explain this statistical result.

All this considered, our study highlights how, despite the success of the vaccination campaign and the availability of early treatments, the risk of developing severe forms of COVID-19 requiring hospitalization is still high, at least for elderly and fragile subjects. Disposing of valid therapeutic alternatives capable of preventing disease progression is fundamental in such cases.

Our results strengthen the evidence that using Baricitinib helps improve the outcomes of patients with moderate/severe COVID-19.

However, our data show that old age, the presence of chronic kidney failure, and the short time of hospital admission from symptom onset often prevent in real life the prescription of Baricitinib in a large part of patients with respiratory failure, who would, instead, benefit from the treatment. Paradoxically, it seems that just the current features of hospitalized patients with COVID-19 are the greater limit to the use of Baricitinib, which is prescribed on a case–by–case basis, according to the individual choice of the clinician.

Further studies with a prospective design, a more significant number of patients, and longer follow-ups are required to design new, different drugs capable of preventing the clinical progression of COVID-19 among fragile subjects who become infected and hospitalized, with the ultimate goal of improving their survival.

Author Contributions: M.P.: formal analysis, writing (original draft, review, and editing); D.L., T.A.S., M.P.F.B., S.L.C.: conceptualization, methodology, writing (review), supervision; M.N., F.D.G.,

G.A.M., T.C., G.G., G.S.: resources, investigation, data curation, writing (review); S.L.C.: project administration. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Having been performed as an observational retrospective study in the context of regular clinical routine, this research did not require formal approval from the ethics committee according to Italian law (art.1, leg. decree 211/2003). The study was conducted following the Declaration of Helsinki and national and institutional standards; data were previously anonymized according to the requirements of the Italian Data Protection Code (leg. Decree 196/2003).

Informed Consent Statement: All patients provided informed consent for using their data for research.

Data Availability Statement: The manuscript has associated data which can be shared in an online repository upon request.

Conflicts of Interest: The authors declare no conflict of interest.

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