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SHORT REPORT

Pronounced benefits of JAK inhibition with baricitinib in COVID-19 pneumonia in obese but not lean subjects

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ABSTRACT

Objective Obesity and age are strongly linked to severe COVID-19 pneumonia where immunomodulatory agents including Janus kinase inhibitors have shown benefits but the efficacy of such therapy in viral pneumonia is not well understood. We evaluated the impact of obesity and age on survival following baricitinib therapy for severe COVID-19.

Methods A post hoc analysis of the COV-BARRIER multicentre double-blind randomised study of baricitinib versus placebo (PBO) with an assessment of 28-day mortality was performed. All-cause mortality by day 28 was evaluated in a Cox regression analysis (adjusted to age) in three different groups according to body mass index (BMI) (<25 kg/m^2, 25–30 kg/m^2 and >30 kg/m^2) and age <65 years and ≥65 years.

Results In the high BMI group (>25 kg/m^2), baricitinib therapy showed a significant survival advantage compared with PBO (incidence rate ratio (IRR) for mortality by day 28 0.53 (95% CI 0.32 to 0.87)) and 0.66 (95% CI 0.46 to 0.94) for the respective <65 years and ≥65 years, respectively. The 28-day all-cause-mortality rates for BMI over 30 were 5.62% for baricitinib and 9.22% for PBO (HR=0.6, p<0.05). For BMI under 25 kg/m^2, irrespective of age, baricitinib therapy conferred no survival advantage (IRR of 1.89 (95% CI 0.49 to 7.28) and 0.95 (95% CI 0.46 to 1.99) for <65 years and ≥65 years, respectively) ((mortality 6.6% baricitinib vs 8.1 in PBO), p>0.05).

Conclusion The efficacy of baricitinib in COVID-19 pneumonia is linked to obesity suggesting that immunomodulatory therapy benefit is associated with obesity-associated inflammation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe COVID-19 induces immunothrombosis in the lungs increasing the disease morbidity.
⇒ Baricitinib was shown to be effective in controlling the COVID-19 disease and reducing overall mortality.

WHAT THIS STUDY ADDS

⇒ The benefit of baricitinib on 28-day-all-cause mortality reduction only showed statistical significance in obese subjects. These findings suggest that the drugs pioneered for rheumatic diseases that show benefit in COVID-19 may not be evident in lean subjects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the link between Janus kinase inhibitors and both venous thrombosis and atherosclerotic disease in the rheumatology setting, the finding of benefit in obese subjects with COVID-19 is paradoxical.
⇒ In lean subjects with COVID-19, these findings suggest a key role for antiviral therapy rather than immunomodulation in disease control.

INTRODUCTION

The recent SARS-CoV-2 virus pandemic has resulted in millions of deaths globally most attributable to severe pneumonia.[1] Pathologically, critical COVID-19 is associated with severe alveolitis but also with diffuse pulmonary vascular immunothrombosis of greater magnitude than influenza pneumonia associated immunothrombosis.[2] Pathologically the clots in severe COVID-19 are rich in immune cells, including netotic neutrophils, macrophages and platelets.[3] The mortality in COVID-19 is associated with obesity and older age, both of which have multifaceted links to inflammation and thrombosis.[4]

Various immunomodulatory therapy including corticosteroids, anticytokine blockers, especially IL-6 blockers and also Janus kinase inhibitors (JAKi), most notably baricitinib where three phases III randomised clinical trials have shown efficacy in COVID-19.[5–7] It remains incompletely understood why these strategies have proved efficacious in the face of potentially active viral pneumonia.

Asides from the SARS-CoV-2 virus itself, obesity and its associated comorbidities have played a major role in mortality in COVID-19

and the 'syndemic' nature of this interaction is well recognised.[8] Indeed, both age-related inflammation and obesity-associated inflammation were well recognised before the COVID-19 pandemic. Our specific hypothesis was that older age and body mass index (BMI), both of which may adversely impact on immunothrombosis, may be associated with better outcomes following JAKi. In this work, we report that the protective effect of baricitinib against death is most pronounced in obese patients which may be significant to immunopathogenesis considerations and therapy selection for disease. Given that obesity is linked to thrombosis in general medicine these findings suggest a JAKi thrombosis paradox in COVID-19, the nature of which requires further research to disentangle.

METHODS

The COV-BARRIER study that was registered at ClinicalTrials.gov, NCT04421027, was an international multicentre, phase III, double-blind, randomised, placebo (PBO)-controlled clinical trial conducted between June 2020 and January 2021 that enrolled 1525 hospitalised COVID-19 adult patients that required baseline oxygen support.[6] The participants received either 4 mg of baricitinib once daily or matched PBO for 2 weeks in addition to the standard therapy (systemic corticosteroids and antivirals, such as remdesivir) with a 1:1 randomisation ratio. The primary endpoints were the progression to high-flow oxygen, non-invasive and invasive ventilation, and death by day 28 and a key secondary endpoints was day 28 all-cause mortality.[6]

Phase III COV-BARRIER study data on all-cause mortality by day 28 was obtained anonymously via Vivli Centre, a non-profit organisation founded to promote global scientific data sharing neutrally by acting as a broker between data contributors and users. Eli Lilly and Company, the data provider, consented to provide the data for our subanalysis.

Given that significant differences were only observed in the secondary endpoint (all-cause mortality by day 28) and not in the primary endpoints within the COV-BARRIER 3 trial, our post hoc analysis primarily focused on day 28 mortality only.

We performed a post hoc analysis and investigated the outcome of mortality by 28 days in different subgroups of age and BMI. Age was categorised into <65 years and ≥65 years, and BMI was categorised into <25 kg/m^2 (normal) and ≥25 kg/m^2 (high). To assess the incidence rate ratios (IRR) of mortality in the different subgroups, we employed the assumption of a Poisson distribution. Complementary all-cause mortality by day 28 was evaluated in a Cox regression analysis was performed and presented graphically. A C reactive protein (CRP)-adjusted model was also conducted.

RESULTS

As previously reported, the all-cause day 28 mortality was 8% (n=62) in the baricitinib arm and 13% (n=100) for PBO, HR 0.57 (95% CI 0.41 to 0.78 (19) .[6] From 1525 patients initially included in the study, 764 were randomised to baricitinib group and 761 to PBO.[6] 30/764 patients in baricitinib arm and 23/761 in PBO arm were not included in our analysis due to missing BMI and/or age data (figure 1).

In our post hoc analysis, we found that within the high BMI group (≥25 kg/m^2) the all-cause day 28 mortality

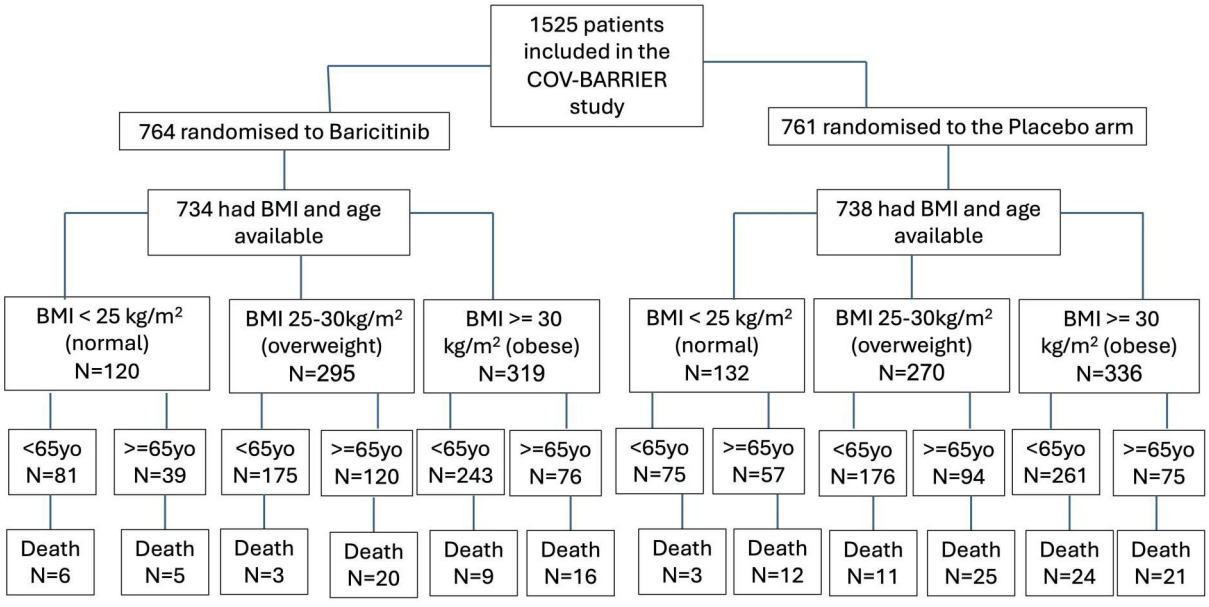

Figure 1 Flow chart of patients included in our post hoc analysis according to BMI group and age. At the end of the COV-BARRIER trial, 159 deaths were reported by day 28; an additional three deaths occurred after the treatment period disposition but within 28 days. 62 in the baricitinib group and 100 in the placebo group. Three of the patients who died in the baricitinib arm and 4 in the placebo arm had no available data on BMI/age and were not included. BMI, body mass index.

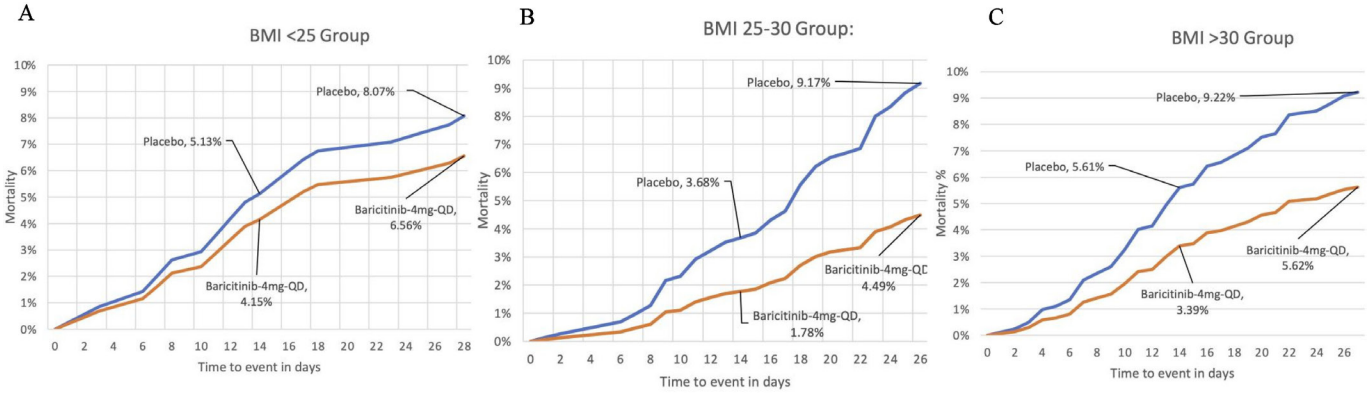

Figure 2 Adjusted 28-day all-cause mortality comparison of baricitinib vs placebo across BMI categories. The figure presents Cox regression curves comparing all-cause mortality rates by day 28 between the placebo (blue line) and baricitinib (orange line) arms in patients with distinct BMI categories (age adjusted). The rates on days 14 and 28 are represented in the graph. (A) In patients with normal BMI, no statistically significant differences were observed between the baricitinib and placebo arms, indicating comparable survival outcomes ((6.56% vs 8.07), p>0.05). (B) In overweight patients (BMI 25–30), the survival curves exhibit a noticeable separation. By day 28, the mortality rate is significantly lower in the Baricitinib group compared with the placebo group (HR 0.47, (4.49% vs 9.17%), p<0.05). (C) In obese patients (BMI>30), the curves further emphasise the distinct impact of Baricitinib. By day 28, the mortality rate is markedly lower in patients receiving baricitinib compared with those on placebo, indicating a potentially critical role of Baricitinib in improving survival outcomes specifically in the obese subpopulation (HR=0.6, (5.62% vs 9.22%), p<0.05). These findings underscore the potential of baricitinib as a targeted therapeutic intervention, particularly beneficial in overweight and obese individuals, and warrant further exploration for personalised treatment strategies. BMI, body mass index.

rates among patients receiving baricitinib were 2.9% (12/418) for individuals <65 years of age and 18.4%% (36/196) for those aged ≥65 years. In the PBO arm, the corresponding mortality rates were 8.8% (35/437) for patients <65 years and 27.2% (46/169) for individuals aged ≥65 years. This yielded an IRR of 0.35 (95% CI 0.19 to 0.68) and 0.67 (95% CI 0.46 to 0.99) for the respective younger and older age categories.

In the normal BMI group, irrespective of age, baricitinib therapy did not show a significant survival advantage when compared with PBO with the mortality rates among patients receiving baricitinib at 7.4% (6/81) for individuals <65 years of age and 12.8% (5/39) for those aged ≥65 years or older. In the PBO arm, the corresponding mortality rates were 4.0% (3/75) for patients <65 years and 21.1% (12/57) for individuals aged ≥65 years. Consequently, the (IRR) was 1.85 (95% CI 0.48 to 7.14) in under 65 years old and 0.61 (95% CI 0.23 to 1.59) in the over 65 age group.

In the age-adjusted Cox regression analysis, patients with a BMI over 30 had significantly lower 28-day mortality in the baricitinib group compared with PBO (HR=0.6 (5.6% vs 9.2%), p<0.05) (figure 2). With adjustment for age, it was noted that BMI values between 25 and 30 that the 28-day mortality had the greatest magnitude of reduction and significantly lower in the baricitinib group compared with PBO (HR=0.47, (4.5% vs 9.2%), p<0.05) (figure 2). However, for patients with BMI lower than 25, the 28-day mortality was not significantly different between the baricitinib group compared with PBO ((6.6% vs 8.1), p>0.05) (figure 2).

After adjusting for CRP levels group with a BMI of 25–30 still had a statistically significant lower 28-day-all-cause mortality within the baricitinib treatment group, but the significance was lost for the BMI >30 group, likely due to a substantial proportion of missing CRP data in this group (21.2%). Further information regarding the missing data and the CRP-adjusted model is available in online supplemental material 1.

DISCUSSION

In this work, we undertook a subanalysis of the COV BARRIER trial and showed improved survival in COVID-19 in obese subjects receiving baricitinib.[6] Most subjects with COVID-19 pneumonia rapidly clear the SARS-CoV-2 virus within the first 20 days, being the clearance particularly faster in younger patients.[9] However, many patients develop critical illness around this time at a stage when adaptive immune responses kick in and augment the magnitude of inflammation that prominently manifests with alveolar and adjacent territory immunothrombosis.[10] The implications of hypoxia are especially relevant in obese subjects where tissue oxygenation is more difficult and where obesity-related inflammation itself is common.[11 12] This suggests that the remarkable emergence of immunomodulatory therapy for viral pneumonia may be contingent on modern 'westernised' diets and lifestyles that link to obesity and that neither mortality of immunomodulatory effectiveness may be prominent in societies with low BMIs.

Obesity itself is closely related to a hypercoagulability state through different mechanisms that include 'fat cytokines', for example, leptin and adiponectin effects, hyperactivity of some coagulation factors such as factor VII and VIII and fibrinogen, and increased levels of

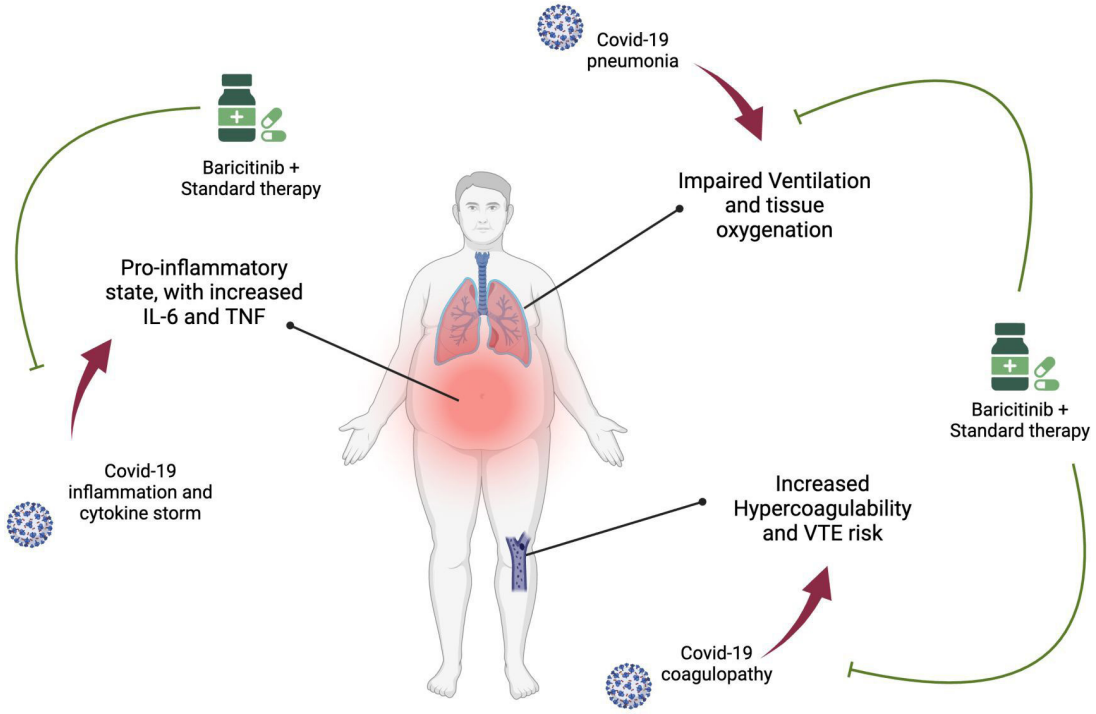

Figure 3 Mechanisms that lead to poor outcomes in obese patients infected with COVID-19 that could explain why this group benefits better from baricitinib therapy. Overall, obese patients may poorly tolerate COVID-19 due to the increased oxygen requirements linked to high BMI and also the proinflammatory impact of obesity on systemic inflammation and exaggeration of virus associated immunothrombosis. Isolated obesity is a well-recognised risk factor for thromboembolism and low-grade inflammation. The obesity defined inflammatory state is associated with increased production of proinflammatory cytokines such as IL-6 and tumour necrosis factor (TNF) and other cytokines. In addition to other comorbidities that invariably accompany obesity, such as diabetes and hypertension, high BMI ventilation impairment that reduces tissue oxygenation. Consequently, the obesity-related proinflammatory state may benefit much more from baricitinib therapy than people with normal BMI. BMI, body mass index.

proinflammatory cytokines. In particular, IL-6 and tumour necrosis factor that are elevated in obesity are also related to immunothrombosis.[13 14] Some mechanisms are exacerbated in obese people and are potentially blocked by baricitinib and other immunomodulatory strategies (figure 3).

Paradoxically, JAKi increases the risk of venous thromboembolism, including the isolated pulmonary embolism (PE) in rheumatoid arthritis (RA).[15] Isolated PE without DVT is also evident in postmortem tissue from fatal COVID-19.[16] However, in COVID-19, baricitinib is used in addition to corticosteroids, which could possibly block this potential prothrombotic effect but more work is needed to understand this. Given that JAK inhibition is actually associated with thrombosis in RA and obesity is linked to thrombosis, our findings are remarkable and suggest a hitherto unappreciated mechanism for this 'JAK thrombosis-related paradox'.

Our study had several limitations. First, our dataset comprised solely the secondary endpoint data from the original COV-BARRIER three study. Consequently, we were unable to ascertain whether our findings could be reproduced for the primary endpoints of COV-BARRIER 3, which encompass progression to high-flow oxygen, non-invasive and invasive ventilation, and death by day 28. Likewise, while investigating the correlation between BMI, CRP levels and mortality in both the PBO and baricitinib arms would be intriguing, we lacked enough data to conduct this analysis (online supplemental file 1). Moreover, the subpopulations had relatively small samples, especially in non-obese younger patients where data interpretation needs to be cautious. Nevertheless, the difference is clear in the Cox regression analysis for survival rates. Still, additional research involving larger cohorts is required to validate this paradoxical effect observed among obese patients and to ascertain its relevance across other medical conditions as well.

The benefit of therapy on mortality was not evident in the normal BMI group. It is well known that very ill COVID-19 patients who succumb to the virus may have ongoing viral replication that can be detected by viral 'RNAaemia' and immunosuppressive therapy with steroids has been detrimental in this group increasing RNAaemia even.[17] This potential negative impact of JAKi in this group is likely offset by the much larger group that has cleared the virus hence the benefits of JAK inhibition at the population level. Further work is needed to address the impact of JAKi and other therapy in this group.

Despite the paradoxical beneficial effect observed in obese COVID-19 patients, there is limited exploration

into obesity's impact on JAKi treatment response in other conditions like RA and Psoriatic Arthritis.[18 19] Studies in these areas suggest obesity may reduce treatment response, contrasting with our current COVID-19 findings. Notably, these studies often use metrics such as the Disease Activity Score (DAS)-28-CRP score. Previously, we identified a subset of RA patients with moderate to high disease activity according to DAS-28-CRP, where approximately 40% showed no signs of synovitis on ultrasound, termed non-inflammatory refractory RA.[20] This subgroup, with a notably higher BMI, might not benefit from alternative therapies, as their symptoms stem from non-active inflammation. This observation could explain the reduced effect of JAKi seen in obese patients compared with COVID-19 cases.

In conclusion, baricitinib is especially efficient in reducing 28-day mortality rates among patients with high BMI, probably because this population has poorer tissue oxygenation and suffers more from COVID-19 immunothrombosis that is controlled when treated with baricitinib and standard COVID-19 therapy. These observations have implications for understanding the place of rheumatologically pioneered drugs in the viral pneumonia arena and suggest that the benefit may be in obese subjects which is somewhat counterintuitive to the use of JAKs in RA where thrombosis may be increased.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Post Hoc analysis of COV-BARRIER study—registered on ClinicalTrials.gov NCT04421027. Data acquired via Vivli Platform—Vivli ID 00008450. Participants gave informed consent to participate in the study before taking part.

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