Short Reports

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Efficacy and safety of deflazacort in diabetic subjects infected with SARS-CoV-2

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ABSTRACT

Background: Different therapies are recommended for the management of COVID-19 at home, use of steroids is the reference for the home management of COVID-19 in second phase of the disease. Several steroids are recommended in the treatment of COVID-19; however, the use of steroids is known to bring to problems in the management of diabetic patients.

Methods: This is a retrospective observational study, conducted with the aim of evaluating the efficacy and safety of the administration of deflazacort in diabetic outpatients infected with SARS-CoV-2, versus standard use of dexamethasone/methylprednisolone.

Results: A total of 63 patients were enrolled: 15 in the "deflazacort" group and 48 in the " dexamethasone/methylprednisolone " group. The study population was 49.2% male with a median age of 63.6 years (IQR 54.5-71.0). 44 (69.8%) patients had at least one comorbidity in addition to diabetes. A total of 4 (6.3%) patients (50% females) required hospital care for glycaemic decompensation, all in the dexamethasone/methylprednisolone group (0 vs 4 p=0.019). Hospitalization occurred in 19 (30.1%) for respiratory failure related to SARS-CoV-2 infection: 5 in the deflazacort group, 14 in the dexamethasone/methylprednisolone group (p=0.76) The mean number of days between illness onset and the first negative swab was 28.4 days in the deflazacort group and 27.4 days in the dexamethasone/methylprednisolone group (p=0.40).

Conclusion: Deflazacort demonstrated a lower incidence of hospital admission for glycaemic decompensation compared to standard treatment with dexamethasone/methylprednisolone in SARS-CoV-2 positive outpatients. There were no differences in COVID-19-related hospitalizations between the two groups.

Key words: COVID-19, corticosteroids, diabetes mellitus, outpatients

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Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the internal institutional review board at the University "G. d'Annunzio" Chieti-Pescara, and all patients provided written informed consent to participate in the study.

Consent for publication: Informed consent was obtained from all subjects involved in this study.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for COVID-19, a disease that in a few months becomes a pandemic starting at the end of 2019. The clinical presentation of this pathology includes fever, fatigue, dry cough, headache, anosmia, dysgeusia, acute lung injury with shortness of breath up to Acute Respiratory Distress Syndrome (ARDS) that can lead the infected patients to death [1-4]. Many factors are associated with severe outcomes from SARS-CoV-2 infection, such as aging, cardiovascular disease, chronic lung disease, diabetes, etc. In fact, in a cohort of outpatients in Italy comorbidity was present in about 61% of patients [3, 5, 6]. Zhou et al. later found diabetes to be the second most prevalent comorbidity (19%), after hypertension (30%), among hospitalised COVID-19 patients [7]. COVID-disease is classically divided into two pathogenic phases: the first is characterized by viral replication [8], the second is linked to the activation of an inflammatory response with the possible appearance of a cytokine storm [9-11]. A rapid and well-coordinated innate immune response is the first line of protection against viral infections, ensuring a less severe second phase of the disease [12-14]. Up to 20% of COVID patients require hospitalization [15-17]; therefore, the focus of most recent research is to try to reduce hospital admissions and therefore patient mortality [5, 8, 10, 18-20].

Different therapies are recommended in the home management of COVID-19. Immunomodulatory agents such as pidotimod or corticosteroids are key during the inflammatory second phase and they are the cornerstone in the outpatient management [5, 11, 21-23]. However, it is known that the use of steroids can causes complication in the management of diabetic patients, such as glycaemic imbalance. The most used and recommended steroids in this setting, are dexamethasone or methylprednisolone, which are among the most powerful steroids and most burdened by metabolic adverse side effects [23-26]. Deflazacort, a synthetic corticosteroid characterized by a methyl-oxazoline ring added to the prednisolone acetate structure, is of particular interest due to its more favourable tolerability and lower glycaemic toxicity [27, 28]; a feature of particular interest in the outpatient setting, where patients cannot receive close monitoring.

We investigated the efficacy and safety of Deflazacort in non-vaccinated diabetic outpatients with SARS-CoV-2 infection, focusing primarily on the rate of hospitalization due to glycemic decompensation. Secondary outcomes included hospitalization for respiratory failure and duration of COVID-19 illness (i.e., days from symptom onset to first negative swab).

Methods and materials

This is a retrospective observational study, conducted at the Clinic of Infectious Diseases of the University 'G. D'Annunzio' - PO SS Annunziata of Chieti enrolling patients' man-aged by Special Units of Continuity of Care (U.S.C.A.) for COVID 19 outpatient. Between January and June 2021, we considered a total of 231 patients with diagnosis of diabetic treated by diet or metformin and with moderate COVID-19. All patients were offered corticosteroids treatment by U.S.C.A. (corticosteroid selection was at the discretion of the physician), in accordance with the local protocols for home management of the COVID-19 patient. The diagnosis was confirmed by PCR in a nasopharyngeal swab and moderate disease was considered present when basal oxygen saturation was ≥ 92% and ≤ 94%, resulting in a needed support with oxygen therapy at home, or post 6 minute walking test oxygen saturation was > 90% and < 94% or there was NSAID-resistant fever for at least 4 days, there wasn't dyspnoea at rest and Modified Early Warning Score (M.E.W.S.) was <6 (Table 1).

Exclusion criteria were: no diagnosis of diabetes mellitus, incomplete medical records, severe/critical COVID-19 disease at the time of enrolment for treatment, hospitalisation for reasons other than COVID-19 or glycaemic control, use of corticosteroids in the absence of moderate COVID-19 (asymptomatic or mild disease patients), treatment with anti-spike monoclonal antibodies, incorrect administration schedule (dose equivalent to less than 6mg dexamethasone at the start of treatment, inconstant

Table 1. Demographic characteristics and symptoms of the patients in this under study.

Gender	
M	31 (49,2%)
F	32 (50,8%)
Age	63,6 (IQR 54.5-71)
Illness Duration	24 (IQR 19.0-33.0)
Comorbidity (+ DM)	
Yes	44 (69.8%)
No	19 (30.2%)
Fever	
Yes	49 (77.8%)
No	14 (22.2%)
Days of Fever	3 (IQR 1.0-6.0)
Symptoms During Disease Course	4.2 (IQR 3.0-5.0)
SpO_2 at enrollment	97%
Minimum SpO_2 During Disease Course	93%
MEWS at enrollment	1 (IQR 0-3)
LUS at enrollment	7 (IQR 4-9.7)
Hospitalization	23 (36,5%)
By glicemic decompensation	4 (6,3%)
By respiratory failure	19 (30.1%)

drug intake) or timing (administration before the first 7 days of disease), aged <18 years old.

The study protocol was approved by the internal Ethics Committee at the University "G. d'Annunzio" Chieti-Pescara.

Study procedures

At the enrollment, demographic characteristics (age, gender), other comorbidities (hypertension, obesity, COPD, etc) and COVID-19 history of disease (presence, type and onset of symptoms, date of positive swab) were recorded; clinical data (respiration rate, peripheral oxygen saturation at rest e during 6 minutes walking test, heart rate, blood pressure, body temperature, chest auscultation, echographic Lung Ultrasound Score (LUS); Modified Early Warning Score (MEWS) were collected during home medical examination and (partially) during daily telephone monitoring of the patient. Deflazacort therapy consisted in oral administration of 45 mg, divided into two daily administrations, until clinical improvement (apyrexia and/or peripheral saturation > 94% at rest or during the 6-minute walking test). The time indication for administration of this molecule was after the first 7 days from the onset of the disease (identified as the earliest between the date of onset of symptoms and the date of first positive swab). As control group included all patients who met the enrollment criteria and who had received, after the first 7 days from the onset of the disease, dexamethasone (6 mg/day once a day) or methylprednisolone (32 mg/day divided into two daily doses), considered as reference corticosteroids in COVID-19.

Statistical analysis

Descriptive analysis was carried out using median and interquartile range (IQR) for the quantitative variables and percentages values for the qualitative ones. The association between endpoint variables (outcome of hospitalizations and duration of the disease) and explicative variables was investigated by Pearson χ^2 test and non-parametric Wilcoxon rank-sum test for unpaired samples or Kruskal Wallis test followed by the appropriate *post-hoc* test if significant. Crude odds ratio (OR) and corresponding 95% CI were calculated to quantify the risk associated with outcome of hospitalizations considered explicative variables using the Wald test. Statistical significance was set at the level of ≤0.05. All analyses were performed using Stata software v17.1 (StataCorp, College Station, USA).

Results

Out of the 231 diabetic patients managed by the USCA between January and June 2021, after the application of exclusion criteria, the elimination of incomplete records and the incorrect treatments (by dosage and timing), 63 patients were enrolled and divided in two groups: 15 in the "Deflazacort" group and 48 in the Dexamethasone/Methylprednisolone group (Figure 1).

The study population made of 49.2% male subjects with a mean age of 63.6 (IQR 54.5-71.0) years.

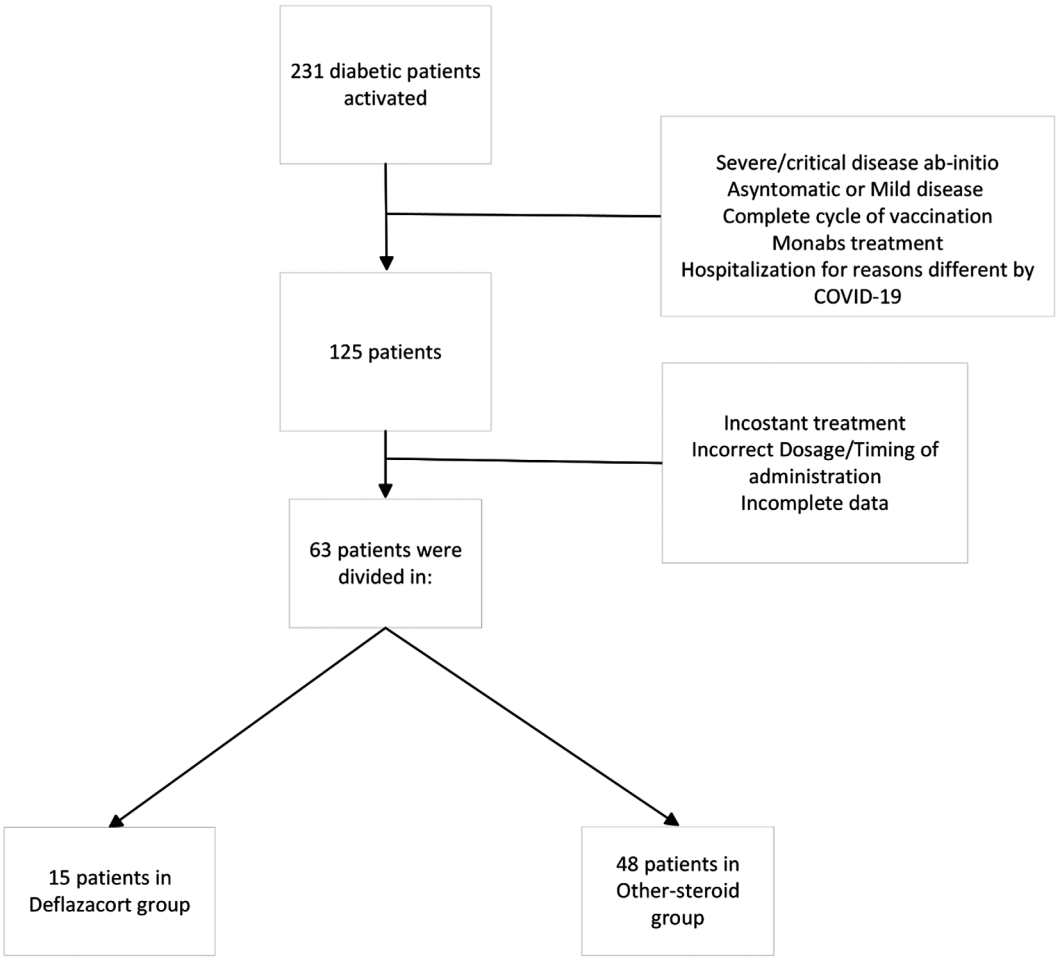

Figure 1. Flow diagram of the patient selection process included in the study.

One comorbidity in addition to diabetes was found in 44 (69.8%) patients. The median of disease duration was 24.0 (IQR 19.0-33.0) days, the median of fever duration was 3.0 (IQR 1.0-6.0) days.

The mean number of symptoms developed during the disease course was 4.2 (IQR 3.0-5.0) symptoms, the median SpO_2 at enrollment was 97% and the median minimum SpO_2 during disease was 93%. The median MEWS score at enrollment was 1 (IQR 0-3), the median LUS at lung ultrasound at enrollment was 7 (IQR 4-9.7); for each group the MEWS score are 1 (IQR 0-2.5) in Deflazacort and 1 (IQR 0-3) in Dexamethasone/Methylprednisolone group the median LUS value was 6.5 (IQR 4-9) in Deflazacort group and 7 (IQR 4-10) in Dexamethasone/Methylprednisolone group (p=0,14).

Hospitalization due to glycemic decompensation occurred in 4 patients (6.3%), all in the Dexamethasone/Methylprednisolone group (0 vs 4; p=0.019) (Table 1).

Regarding secondary endpoints, hospitalization for respiratory failure due to COVID-19 disease and duration of the disease, we found that 19 patients (30.1%) required hospitalization for respiratory failure related to SARS-CoV-2: 5 in the Deflazacort group, 14 in the Dexamethasone/Methylprednisolone group (p=0.76). The mean number of days between the onset of the disease and the first negative swab was 28.4 days in the Deflazacort group and 27.4 in the Dexamethasone/Methylprednisolone group (p=0.40) (Table 2).

No significative difference was found in secondary outcomes. No other side grade 3-4 side

Table 2. Characteristics of hospitalized patients with and without deflazacort therapy.

Deflazacort Therapy			
	No (n = 48)	**Yes (n =15)**	**P**
Hospitalization			
By glicemic decompensation	4 (8.3%)	0 (0%)	0.019
By respiratory failure	14 (29.2%)	5 (33%)	0.76
Illness Duration	27.4 (11-70)	28.4 (17-42)	0.40

effect was recorded. No hospitalized patient developed tuberculosis.

Discussion

This study demonstrates a significantly lower rate of glycaemic-related hospitalization in diabetic COVID-19 outpatients treated with Deflazacort compared to those receiving Dexamethasone or Methylprednisolone Though nearly four years have passed since the emergence of SARS-CoV-2, the virus remains a challenge, particularly in managing vulnerable outpatient populations. The clinical spectrum of this infection ranges from asymptomatic to severe disease with refractory hypoxemia requiring invasive mechanical ventilation, and death. Mass COVID-19 vaccination has allowed to obtain lower clinical pictures and to manage more patients at home. This has made home management of COVID-19 patients increasingly common; the availability of monoclonal anti-bodies and antivirals goes in this direction, providing effective, but expensive and time-dependent treatments [5, 8, 29, 30]. Despite this, most studies on COVID-19 disease concern hospitalized patients, only a few studies investigate home management after the first 7 days from the onset of COVID-19 disease [30-33]. An alternative approach based on early moderation of the inflammatory response, is use of pidotimod, that could directed toward a more efficient, coordinated and appropriate response and it has demonstrated a reduction in hospitalization and in steroid use [5, 21, 34]. When other approaches fail and the patients enters into an aggressive second phase of disease, steroids are considered the cornerstone in the COVID-19 outpatients [5, 21, 23] . The use of steroids was considered as an option in patients after the first phase of the disease who did not recover or who had mild respiratory failure, this to improve the cytokine cascade typical of the second phase of the disease. Corticosteroids have an immunosuppressive and anti-inflammatory action mainly related to the antagonism of the specific function of leukocytes and the inhibition of the synthesis of proinflammatory cytokines [35, 36], which explains the main reason for their use in the second phase of COVID-19; in fact several studies have demonstrated the role of corticosteroids in the treatment of COVID-19 [37]. Several steroids are considered effective in treating COVID-19 (dexamethasone, methylprednisolone, prednisolone…), but each is known to cause problems in managing patients. In fact, corticosteroids activated same glucocorticoid receptor that is responsible in metabolic and anti-inflammatory effect [37-40]. Adverse effects related to steroids, especially affect some population groups: the elderly (in whom the risk of side effects of corticosteroids can be increased by greater comorbidity and the intake of other drugs), hypertensives, heart patients, osteoporotic, diabetic patients. The same groups of patients are those at high risk of negative outcome of SARS-CoV-2 infection and, therefore, require more frequent treatment with steroids.

Particular attention must be paid to patients suffering from alterations in glucose metabolism, who are particularly affected by the negative effects of steroids; in fact, in the outpatient's management of COVID-19, as continuous and close monitoring is not possible, glycaemic decompensation can be particularly hard to recover. Extremely interesting seems to show that the use of deflazacort causes minor glucose alterations, therefore none of the diabetic patients in the study required hospitalization for glucose decompensation. This is a distinctive feature of deflazacort that cause smaller influence on carbohydrates metabolism versus other glucocorticoids, such as demonstrated in other condition in both studies conducted on animal and clinical trials [41-43]. Besides, this high tolerability of deflazacort did not affect the effectiveness of the steroid's immunoregulatory action. In fact, no differences emerged in the

two groups regarding the due to respiratory impairment due to COVID-19. Deflazacort exerts anti-inflammatory and immunomodulatory effects through mechanisms similar to other corticosteroids (e.g., NF-κB inhibition, cytokine suppression), but has a unique structure that leads to lower hepatic glucose production and less insulin resistance [40, 44]. This balance likely explains its efficacy in controlling inflammation without significantly worsening glycemia. Several studies have demonstrated the efficacy of deflazacort compared to other steroids in different clinical conditions, much to establish correct equipotency ratio deflazacort/prednisone 1,2/1 [45]. Several studies have shown that the use of corticosteroids for COVID-19 presents the potential risk of facilitating the onset of other quiescent diseases, such as the reactivation of latent tuberculosis. The exposure time is crucial for this risk. In COVID-19 outpatients, the use of corticosteroids is limited to a period of less than 10 days, which makes this risk negligible; in fact none of our patients showed signs of tuberculosis [46-49].

We are aware that limitation of our study is mainly due to the small sample, and we lack on long time follow up which could be reduce generalizability; therefore, the retrospective design of the study could be limit the ability causality. Furthermore, our patients are all unvaccinated and we lack on long time follow up. This is the first report evaluating the efficacy and safety of Deflazacort administration in SARS-CoV-2 infected, not vaccinated, diabetic subject, in order to reduce the numbers of hospitalization by glycaemic decompensation without loss of efficacy for COVID-19 progression, so the results of this study should be considered for investigation in future large studies.

Conclusion

Deflazacort showed a significantly lower incidence of hospitalization due to glycaemic decompensation compared to dexamethasone/methylprednisolone in SARS-CoV-2 positive diabetic outpatients, with no differences in respiratory outcomes.

It may represent a valuable option in the outpatient management of COVID-19 in patients with glucose metabolism disorders.

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