REAL-LIFE COMPARISON OF TOCILIZUMAB AND ANAKINRA ASSOCIATED WITH CORTICOSTEROID USE IN A COHORT OF HOSPITALIZED PATIENTS WITH SARS-CoV-2 INFECTION

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Abstract
COVID-19 treatment includes both antiviral agents and immunosuppressive and immunomodulatory medication for moderate and severe disease, which decrease systemic inflammation. Our objective was to evaluate tocilizumab, anakinra and corticosteroid effectiveness in a cohort of COVID-19 patients hospitalized in a tertiary care unit from Bucharest, Romania, during the second and third SARS-CoV-2 pandemic waves, by assessing the prediction variables for the length of hospital stay (LHS). We enrolled 330 consecutive patients, with a mean age of 58.2 ± 14.8 years, 119 females (mean age 61.4 ± 14.1 years) and 211 males (mean age 56.4 ± 15 years). The prediction parameters for LHS were the treatment approach, older age and the presence of COPD, but were not associated with other significant comorbidities for COVID-19, such as obesity, diabetes, chronic renal failure or active malignancy. We found a significant difference in the mean LHS between patients who received tocilizumab and standard of care and patients treated with anakinra plus standard of care. Still, this difference was only seen in patients who required high concentration oxygen therapy (more than 5 L/minute). We suggest that, especially in non-critically-ill patients with a high oxygen therapy requirement, the administration of tocilizumab and standard of care is associated with a reduced length of hospital stay compared to the anakinra standard of care regimen.

Rezumat
Tratatul formelor moderate și severe de COVID-19 include atât agenți antivirali, cât și medicamente imunosupresoare și imunomodulatoroare, care scad inflamația sistemică. În acest studiu, obiectivul nostru a fost să evaluăm eficacitatea tratamentului cu tocilizumab comparativ cu anakinra, administrate în asociere cu corticosteroizi, într-o cohortă de pacienți cu COVID-19 internați într-o unitate de îngrijire terțiară din București, România, în timpul celui de-al doilea și al treilea val pandemic, prin evaluarea variabilelor predictibile pentru durata spitalizării (length of hospital stay, LHS). Am înrolat 330 de pacienți internați consecutiv, cu o vârstă medie de 58,2 ± 14,8 ani, 119 de sex feminin (vârsta medie 61,4 ± 14,1 ani) și 211 de sex masculin (vârsta medie 56,4 ± 15 ani). Factorii predictibili pentru LHS au fost abordarea terapeutică, vârsta înaintată și prezența BPOC, dar nu a fost asociată cu alte comorbidități semnificative pentru COVID-19, cum ar fi obezitatea, diabetul, boală cronnică de rinichi sau neoplaziile active. Am găsit o diferență semnificativă a duratei mediei de spitalizare între pacienții care au primit tocilizumab și standard of care și pacienții tratați cu anakinra plus standard of care, dar această diferență a fost observată numai la pacienții care au necesitat oxigenoterapie cu debit mare (mai mult de 5 L/minute). Rezultatele sugerează că, în special la pacienții non-critici, cu un necesar mare de oxigenoterapie, tratamentul cu tocilizumab și standard of care se asociază cu o durată mai redusă a spitalizării, comparativ cu administrarea tratamentului standard plus anakinra.

Keywords: COVID-19, tocilizumab, anakinra, SARS-CoV-2
both associated with COVID-19, which can lead to or exacerbate ARDS and multiorgan failure [11]. COVID-19 treatment includes antiviral agents that inhibit SARS-CoV-2 replication, such as remdesivir, and immunosuppressive and immunomodulatory drugs that reduce systemic inflammation [15]. Corticosteroids and targeted cytokine blocking molecules, such as IL-6R antagonists and IL-1 inhibitors, are most commonly used for this purpose. Additionally, anticoagulant therapy should also be initiated because of the hyper-coagulability state associated with this disease [17]. Anakinra, an IL-1 antagonist, is a promising treatment option for COVID-19, as it has been proven safe and could reduce the need for invasive mechanical ventilation and mortality risk. Anakinra should be administered early in the course of the disease to patients who have elevated inflammatory markers such as CRP and ferritin since studies have shown that anakinra was more effective in lowering mortality risk in patients with CRP > 100 mg/L and ferritin > 1000 ng/mL [1].

Tocilizumab, an anti–IL-6 receptor monoclonal antibody used to treat various inflammatory disorders, is recommended as an off-label treatment after observational studies showed it improved outcomes in patients with COVID-19 pneumonia. On the other hand, randomized trials of tocilizumab have yielded conflicting results in patients with varying degrees of COVID-19 disease severity and populations with various background standards of care [15]. Given the findings of the most recent studies, the question of which of these two immunomodulating agents is preferable emerges [1]. Our aim was to evaluate and compare the effectiveness of tocilizumab, anakinra and corticosteroid use in a cohort of COVID-19 patients hospitalized in a tertiary care unit from Bucharest, Romania, during the second and third SARS-CoV-2 pandemic wave, by evaluating the variables that predicted the length of hospital stay.

Materials and Methods

We performed a retrospective cohort study, including data from the medical records of consecutive patients admitted to “C XI” department of “Prof. Dr. Matei Bals” National Institute of Infectious Diseases, Bucharest, Romania, from February 1st 2021 to 31st of May 2021. All patients had a positive rapid antigen test or reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2, analysed from nasopharyngeal swab specimens. We excluded patients with confirmed SARS-CoV-2 infection, requiring orotrachael intubation for invasive mechanical ventilation at admission. We selected all clinical records of patients aged over 18 years, in consecutive order, treated in our department, and included for analysis: age, gender, body mass index (BMI), presence of obesity, significant clinical history (hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal disease, active malignancy, autoimmune disease, chronic hepatic disease), COVID-19 signs and symptoms, oxygen therapy requirement, treatment during hospitalization, length of hospital stay. Our endpoint was the length of hospital stay (LHS). The ethics committee of “Prof. Dr. Matei Bals”, National Institute of Infectious Diseases, Romania, approved the study protocol (C0409/2021).

Statistical analysis

The variables with Gaussian distribution were presented as means (± standard deviation [SD]). We used an independent-sample t-test to evaluate the differences in means between these groups; 95% confidence intervals for differences between means were also calculated. The Chi-square test was used for testing the statistical significance in categorical variables tables. Linear or logistic regression models were used in the univariate and multivariate analysis. The statistical significance cut-off point was set at 5%. We performed all analyses with SPSS® Statistics v.22.0, IBM®, New York, USA.

Results and Discussion

We enrolled 330 consecutive patients, with a mean age of 58.2 ± 14.8 years, the age ranged from 21 to 92 years, including 119 females (mean age 61.4 ± 14.1 years) and 211 males (mean age 56.4 ± 15 years). Five patients (1.5%) necessitated orotracheal intubation for mechanical ventilation, and 4 patients (1.2%) died. All other patients were discharged after a mean LHS of 10.4 ± 5.4 days (range 1 - 46 days). One hundred and forty-six patients (44.2%) necessitated no oxygen therapy on admission, and 96 (29.1%) remained without oxygen therapy until discharge (NO group). Ninety-three (28.2%) patients had a low concentration oxygen (LCO) therapy requirement during hospitalization (1 to 4 L/minute), and 141 (42.7%) had a high need (HCO) (more than 5 L/minute). Forty-five patients (13.6%) received no corticosteroids or immunomodulatory treatment (NOT group). The standard of care treatment (SC) for patients with oxygen requirement consisted of corticosteroids plus anticoagulation; most individuals (152 – 46.1%) in our cohort received SC. In the tocilizumab group, we included the persons treated with tocilizumab plus SC – TCZ-SC group – 38 patients (11.5%), and the ANK-SC group included 67 patients (20.3%) who received anakinra plus SC. Twenty-eight (8.5%) patients were treated with tocilizumab plus anakinra plus corticosteroids (TCZ-ANK-SC group). The mean length of hospital stay was 7.8 ± 4.3, 9 ± 4, 10.2 ± 4.5, 11.9 ± 5.2 and 15.8 ± 9.1 days for NOT, SC, TCZ-SC, ANK-SC and TCZ-ANK-SC groups, respectively (Table I).
LHS was predicted by the type of treatment group (r = 0.342, p = 0.00), older age (r = 0.331, p = 0.00), the presence of hypertension (r = 0.215, p = 0.00) and COPD (r = 0.193, p = 0.00), in the univariate analysis. In the multivariate analysis, only the treatment group, older age and the presence of COPD predicted the LHS (r = 0.481, p = 0.00).

LHS was not influenced by the smoker status (r = 0.062, p = 0.26), gender (r = 0.002, p = 0.96), body mass index (r = 0.004, p = 0.93), the presence of obesity (r = 0.043, p = 0.44), diabetes (r = 0.09, p = 0.08), chronic renal failure (r = 0.099, p = 0.074), autoimmune disease (r = 0.031, p = 0.58), chronic hepatic disease (r = 0.22, p = 0.69) or active malignancy (r = 0.02, p = 0.97).

In subgroup analysis, a significant difference between the tocilizumab and anakinra treatment groups was only observed in HCO patients: 9.7 ± 5.4 days in TCZ-SC (30 patients) vs. 13.2 ± 6.1 for ANK-SC (40 patients), p = 0.01. For the LCO group, we observed no significant differences: 8.6 ± 2.3 days for TCZ-SC vs. 10.1 ± 3.1, p = 0.3.

In our cohort, the LHS was significantly predicted by the treatment group, older age, and COPD presence. We found a significant difference in the mean LHS between patients who received tocilizumab and standard of care (TCZ-SC) and patients treated with anakinra plus standard of care. Still, this difference was only seen in patients who required high concentration oxygen therapy (more than 5 L O_2/min). As expected, LHS was predicted by older age and the presence of COPD and was correlated with hypertension in the univariate analysis, but, interestingly, it was not associated with other significant comorbidities for COVID-19, such as obesity, diabetes, chronic renal failure or active malignancy.

Many previous studies have attempted to assess the benefit of anti-interleukin drugs in COVID-19, but the results are still contradictory.

On June 24th, 2021, the FDA granted Actemra® (tocilizumab) an emergency use authorization (EUA) for the treatment of hospitalized adults and paediatric patients (2 years and older) who are clinically deteriorating despite receiving systemic corticosteroids and oxygen therapy such as non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Actemra®’s EUA is based on the results of multiple clinical trials, with the RECOVERY and the EMPACTA trials providing the most relevant scientific data on Actemra®’s potential usefulness for its authorized use [5].

In the RECOVERY trial, 4,116 hospitalized patients with severe COVID-19 pneumonia were randomized to receive either Actemra® plus usual care (2,022 patients) or standard care alone (2,094 patients). The primary endpoint was death after 28 days of follow-up, and the preliminary analysis results yielded statistically significant results. Patients receiving Actemra® had a 30.7 percent chance of dying by day 28 compared to 34.9 percent for patients receiving standard care alone. Those taking Actemra® had a median duration to hospital discharge of 19 days, compared to more than 28 days for patients receiving standard care alone [5].

In the IMPACT trial, 389 hospitalized patients with COVID-19 pneumonia were randomized to receive Actemra® (249 patients) or placebo (128 patients). Through 28 days of follow-up, the primary endpoint assessed the requirement for mechanical ventilation or death. When comparing patients who received Actemra® to those who received placebo, there was a statistically significant reduction in progression to mechanical ventilation or mortality for those who

| Table I | Epidemiological and clinical history characteristics of enrolled patients, divided by treatment groups |
|--------|-------------------------------------------------|
|        | Total patients | NOT | SC | TCZ-SC | ANK-SC | TCZ-ANK-SC | p    |
| Frequency (percent) | 330 | 45 (13.6) | 152 (46.1) | 38 (11.5) | 67 (20.3) | 28 (8.5) |
| LHS (days) | 10.4 ± 5.4 | 7.8 ± 4.3 | 9 ± 4 | 10.2 ± 4.5 | 11.9 ± 5.2 | 15.8 ± 9.1 | 0.00* |
| Age (years) | 58 ± 14.8 | 50 ± 16.7 | 58.7 ± 13.3 | 57 ± 15.3 | 60.6 ± 14.5 | 59.6 ± 16.1 | 0.07 |
| Males/females ratio | 1.77 | 2.21 | 1.45 | 2.45 | 1.31 | 8.33 | 0.00* |
| BMI (kg/m²) | 29.1 ± 5.5 | 27.5 ± 7.7 | 29.1 ± 5.3 | 29.1 ± 5.1 | 29.6 ± 4.6 | 30.7 ± 4.7 | 0.03* |
| Obesity | 127 (38.5) | 13 (28.9) | 57 (37.5) | 13 (34.2) | 31 (46.3) | 13 (46.4) | 0.33 |
| COPD | 8 (2.4) | 2 (4.4) | 3 (2) | 2 (5.3) | 3 (2) | 1 (3.6) | 0.40 |
| Hypertension | 164 (49.7) | 14 (31.1) | 81 (53.3) | 16 (42.1) | 37 (55.2) | 16 (57.1) | 0.05 |
| Diabetes Mellitus | 58 (17.6) | 8 (17.8) | 26 (17.1) | 10 (26.3) | 8 (11.9) | 6 (21.4) | 0.43 |
| COPD | 9 (2.7) | 0 | 4 (2.6) | 0 | 1 (1.5) | 4 (14.3) | 0.00* |
| Chronic renal failure | 18 (5.5) | 1 (3) | 6 (3.9) | 2 (5.3) | 4 (6) | 3 (10.7) | 0.67 |
| Chronic hepatic disease | 23 (7) | 6 (13.3) | 6 (3.9) | 1 (2.6) | 5 (7.5) | 5 (17.9) | 0.02* |
| Autoimmune disease | 9 (2.7) | 2 (4.4) | 4 (2.6) | 1 (2.6) | 2 (3) | 0 | 0.86 |
| Active malignancy | 15 (4.5) | 1 (2.2) | 7 (4.6) | 1 (2.6) | 5 (7.5) | 1 (3.6) | 0.68 |

Data are shown as mean ± standard deviation or number (percent). NOT - no corticosteroids or immunomodulatory treatment group; SC – standard of care group; TCZ-SC – tocilizumab plus standard of care group; ANK-SC – anakinra plus standard of care group; TCZ-ANK-SC – tocilizumab plus anakinra plus standard of care group.

* p < 0.05 for linear or logistic regression analysis.
received Actemra®. By day 28, the proportion of patients who required mechanical ventilation or died was predicted to be 12.0% for Actemra® and 19.3% for placebo [5].

Rosas’ group revealed the results of its phase 3 clinical trial (COVACTA) in February 2021. This was an international, randomized, double-blind, placebo-controlled trial carried out in 62 hospitals across nine countries in the United States and Europe. Patients with severe COVID-19 infection were randomized 2:1 to receive a single intravenous infusion of tocilizumab 8 mg/kg vs. placebo. In this study, no further advantage of tocilizumab in mortality or improvement in clinical status according to the ordinal severity scale at 28 days was found. However, it appears that hospitalization and ICU stay times were reduced in the therapy group [14].

Vijairam Selvaraj et al. searched electronic databases between March 1st, 2020 and February 28th, 2021, for randomized controlled studies that assessed the efficacy of tocilizumab in hospitalized COVID-19 patients. All-cause mortality at 28 days, mechanical ventilation, and time to discharge were all considered. The meta-analysis included eight studies with a total of 6311 subjects. Tocilizumab was given to 3267 individuals, while usual care/placebo was given to 3044. Compared to standard care or placebo, the tocilizumab arm had a significantly lower risk of all-cause mortality and progression to mechanical ventilation at 28 days. In addition, there was a trend toward a shorter median stay in the hospital [16].

In the REMAP-CAP trial, tocilizumab was administered to 353 COVID-19 patients within 24 hours of initiating organ support therapy in the intensive care unit (ICU), and 402 patients received a placebo. Because glucocorticoids were given to more than 80% of the patients, the research considered potential treatment-by-treatment interactions. The tocilizumab group had a median number of organ support-free days of 10 instead of 0 days in the control group. The treated individuals had a 27 percent in-hospital mortality rate compared to 36 percent in the control group. The combined effect of tocilizumab and glucocorticoids was more potent than either intervention independently [13].

In a meta-analysis conducted by Barkas’s group, which included nine studies (n = 1119), the conclusion was that anakinra reduced the need for invasive mechanical ventilation and mortality risk compared with standard of care therapy. There were no significant differences regarding the risk of adverse events, including liver dysfunction and bacteraemia [2].

In a meta-analysis of six studies involving 895 patients, Evdokia Kyriazopoulou et al. discovered that mortality was considerably lower in anakinra-treated patients with moderate-to-severe COVID-19 pneumonia, especially in the presence of hyper inflammation indicators such as CRP > 100 mg/L. Mortality was markedly lower in anakinra-treated patients (11.1%) than in patients receiving standard-of-care and/or placebo on top of standard-of-care (24.8%) [8].

In 2021, Bozzi et al. investigated a combination of methylprednisolone (MP) and anakinra in 120 COVID-19 patients with hyperinflammation. Sixty-five of these patients were given anakinra and methylprednisolone, while the other 55 were untreated historical controls. At 28 days, treated patients had a mortality rate of 13.9 percent, while controls had a mortality rate of 35.6 percent. There were no significant differences in bloodstream infections or laboratory changes [3].

SAVE-MORE is a randomized controlled trial that investigated the efficacy and safety of anakinra in 594 individuals with COVID-19 who were at risk of developing respiratory failure. 85.9% (n = 510) of whom were on dexamethasone. On day 28, the median WHO-CPS decreased by 4 points in patients receiving anakinra compared to only 3 points in the placebo group. On day 7, the Sequential Organ Failure Assessment SOFA score decreased by a median number of 0 in the placebo group and 1 in the anakinra-receiving group. Patients who received anakinra had a lower 28-day death rate and spent less time in the hospital [9].

Few studies have compared the benefits of IL-1 vs. IL-6 inhibitors. As far as we know, the most extensive study in this regard was published in March 2021 by Narain et al. and included 5,776 patients. They showed a higher survival rate in patients receiving corticosteroids in combination with tocilizumab than in patients receiving corticosteroids alone or combined with anakinra [10]. Furthermore, a randomized controlled trial by REMAP-CAP investigators, published in June 2021, also showed the superiority of IL-6 blockade over IL-1 blockade in a group of 2,274 critically ill patients with COVID-19 [13].

One of this study's strengths is the fact that it is, to the best of our knowledge, the first study of such kind carried out in Romania, and one of the first few studies carried out worldwide that tried to compare the effect of these two immunomodulators. Another study strength is that we used corticotherapy as a standard of care, while most studies to date, although recently published, have enrolled patients treated before the widespread use of corticosteroids. Thus, the standard treatment in these patients was often hydroxychloroquine and other drugs that have been shown to have no benefit in COVID-19 [4]. This is important to consider, as corticosteroid therapy appears to have a synergistic effect with interleukin inhibitors [12].
One of the study limitations is the lack of a standardized
dose of anakinra. While for tocilizumab, the dose of
8 mg/kg (with a maximum dose of 800 mg) given
as a single dose or repeated once after 12 - 24 hours
is the most commonly used [13], for anakinra, there
are multiple dosage regimens used in various clinical
trials, ranging from low to high dose and from intra-
venous to subcutaneous administration. To facilitate
the comparison process, we prefer using a cumulative
dose that ranges from 100 mg to 2700 mg sub-
cutaneously.

Another limitation is the small number of patients
included in the study. More research is needed, including
studies carried on extensive groups of patients, such
as prospective, randomized trials, which can support
the medical community to draw a conclusion and
elaborate updated guidelines in the foreseeable future.
Multiple studies on this subject continue to be carried
out. Current guidelines recommend treating patients
with remdesivir in the viral phase and dexamethasone,
tocilizumab or baricitinib in the inflammatory phase.
The variable outcomes of the anakinra trials under-
score the issues with small clinical trials that provide
ambiguous results since treatment benefits may only
be seen in select subgroups of patients or during specific
phases of the disease. Another possible reason for
the contradictory results of some studies regarding
anakinra is the different doses of drugs administered,
as there is no standardized dose/duration of treatment
at present.

Conclusions
Our study did not include critically ill patients. It
provides real-life data from a non-ICU department,
representing the most inpatients during Romania’s
second and third SARS-CoV-2 pandemic wave. The
length of hospital stay was significantly predicted by
the treatment group, older age, and COPD, but was not
influenced by other known significant comorbidities.
Our data suggest that, especially in patients with a high
oxygen therapy requirement, who necessitated more
than 5 L O2/min, the administration of tocilizumab
and standard of care was associated with a reduced
length of hospital stay when compared to the anakinra-
standard of care regimen.

Conflict of interest
The authors declare no conflict of interest.

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