Beneficial of adding Tocilizumab to standard care in critical forms of Covid-19 pneumonia: Study on paired series

Bénéfice de l'adjonction du Tocilizumab aux soins standards dans les formes critiques du Covid-19 : étude sur séries appariées

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RÉSUMÉ

Introduction : Le tocilizumab (TCZ), un anticorps monoclonal humanisé dirigé contre les récepteurs de l'interleukine-6 (IL-6), a été essayé dans de nombreuses études en tant que thérapeutique anti Covid-19 avec des résultats controversés.

Objectif : Nous avons cherché à évaluer l'efficacité de l'ajout de TCZ aux soins standard (SS) chez les patients critiques atteints par la Covid-19.

Méthodes : étude rétrospective comparative sur deux séries appariées de patients critiques atteints de Covid-19 : le 1er groupe a reçu TCZ plus SS versus un 2ème groupe qui a reçu uniquement les SS. Les critères d'appariement étaient l'âge, le sexe et le score de sévérité et l'appariement était basé sur le score de propension d'appariement (SPA) par le plus proche voisin. Les critères de jugement étaient : la survie, la ventilation mécanique (VM) et les infections nosocomiales.

Résultats : Quatre-vingt-dix patients ont été inclus par appariement estimé réussi (SPA > 0,5 dans plus de 50 % de chaque groupe pour tous les critères d'appariement). 55,5 % des patients du groupe SS ont évolué vers le stade 3 du syndrome de détresse respiratoire aiguë (SDRA) versus 31 % des patients TCZ + SS (p=0,03). Aucun effet de l'adjonction du TCZ n'a été retrouvé sur la mortalité (49% dans chaque groupe, p=1) ni sur l'utilisation de la VM (p=0,67). Le séjour en USI était plus prolongé dans le groupe TCZ+SC (16 versus 8 jours, p<10-3). L'administration de TCZ a induit une diminution significative de la CRP mais n'a pas modifié le dosage d'IL-6. Des infections nosocomiales étaient survenues chez 18 (40 %) du groupe TCZ+SS comparativement à 15 (33,5 %) du groupe SS, p = 0,66.

Conclusion : Le tocilizumab a réduit le risque d'évolution vers un SDRA sévère probablement grâce à ses propriétés immuno-modulatrices. Mais aucun effet bénéfique n'a été retrouvé sur la survie ni sur le recours à la ventilation.

Mots-clés : Covid-19, Réanimation, Mortalité, SDRA, Ventilation mécanique, Tocilizumab.

ABSTRACT

Introduction: Tocilizumab (TCZ), a humanized monoclonal antibody directed against interleukin-6 (IL-6) receptors, has been tried in various studies as a Covid-19 therapy with controversial results.

Aim: To evaluate the effectiveness of adding TCZ to standard care (SC) in critical Covid-19 patients.

Methods: it was designed retrospectively as a comparative study on two paired series of critical patients affected with Covid-19: the 1st group received TCZ plus SC versus a 2nd group which received only SC. The matching criteria were age, sex and severity score and the matching was based on the propensity score matching (PSM) by the nearest neighbor. Outcomes were: survival, mechanical ventilation (MV) and nosocomial infections.

Results: Ninety patients were included by pairing estimated successful (PSM > 0.5 in more than 50% in each group for all matching criteria). 55.5% of SC group progressed to stage 3-acute respiratory distress syndrome (ARDS) versus 31% of TCZ+SC patients (p=0.03). No effect of TCZ was found on mortality (49% in each group, p=1) nor on MV use (p=0.67). ICU stay was more prolonged in TCZ+SC group (16 versus 8 days, p <10-3). The administration of TCZ induced a significant decrease in CRP but not changed the IL-6 dosage. Nosocomial infections occurred in 18 (40%) of TCZ+SC group comparatively to 15 (33,5%) of SC group, p=0.66.

Conclusion: Tocilizumab reduced the risk of progression to severe ARDS probably due to its immune-modulating properties. But no beneficial effect was found on survival or on the use of ventilation.

Keywords: ARDS, Covid-19, Critical care, Mortality, Mechanical ventilation, Tocilizumab.

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INTRODUCTION

Tocilizumab (TCZ), a humanized monoclonal antibody directed against interleukin-6 (IL-6) receptors, has been the subject of several trials in anti-corona virus disease (Covid-19) therapies with controversial results. The last meta-analysis carried out by the world health organization (WHO) working group established a survival benefit including critically ill patients [1]. In Tunisia, the effectiveness of TCZ in critical forms of Covid-19 remains an unresolved question in terms of cost-benefit. We aimed to assess the effectiveness of adding TCZ to standard care in patients hospitalized in intensive care units (ICUs) for a critical form of Covid-19.

METHODES

A retrospective comparative study on two paired series of critical patients affected with Covid-19: the first group received TCZ in addition to standard care (SC) versus a second group which received only SC. SC included oxygen therapy as needed (high flow nasal cannula, non-invasive ventilation or mechanical ventilation (MV)), prone position, dexamethasone 6 mg / day, anticoagulation (curative in the event of thromboembolic complications), vitamin support and gastro protection by proton pump inhibitor.

TCZ was administered intravenously at single dose of 8 mg / kg or double dose according to the judgment of the practitioners in charge and the dosage of IL-6. The 2 groups were selected by pairing and the pairing criteria were age, sex and initial severity estimated by the simplified acute physiology score II (SAPS II).

The matching was based on the propensity score matching (PSM) by the nearest neighbor (a patient from the TCZ+SC group is matched with a patient from the control group based on the closest propensity score). It was considered as a matching success; when the majority of patients (>50%) in each group had a PSM >0.5 for each pairing criteria.

Basic clinical data related to respiratory distress such the respiratory rate (RR), respiratory muscle use, frequency and response to awake prone position (APP) were also collected. The poor response to APP was defined by the requirement of MV.

Outcomes were: the maximum severity of the acute respiratory distress syndrome (ARDS) reached by the patient, i.e. stage 3 of the ARDS, survival, requirement of MV, ICU related infections and others. ARDS was diagnosed as distinguished by the 2012 Berlin definition [2]: presence within seven days of acute pulmonary or extra-pulmonary pathology of the association of acute hypoxemia ($PaO2/FiO2 \leq 300$ mm Hg) in a ventilated patient with a positive expiratory pressure (PEEP) of at least 5 cm H2O, as well as bilateral radiological infiltrates not fully explained by heart failure or volume overload. ARDS severity was classified according to the P/F ratio into mild ARDS or stage 1 ($200 < P/F \leq 300$ mm Hg), moderate ARDS or stage 2 ($100 < P/F \leq 200$ mm Hg) and severe ARDS or stage 3 ($P/F \leq 100$ mmHg).

Nonparametric tests of paired series were used for the comparisons: McNemar's test for binary variables and Wilcoxon's test for continuous quantitative variables. The propensity score was calculated by logistic regressions.
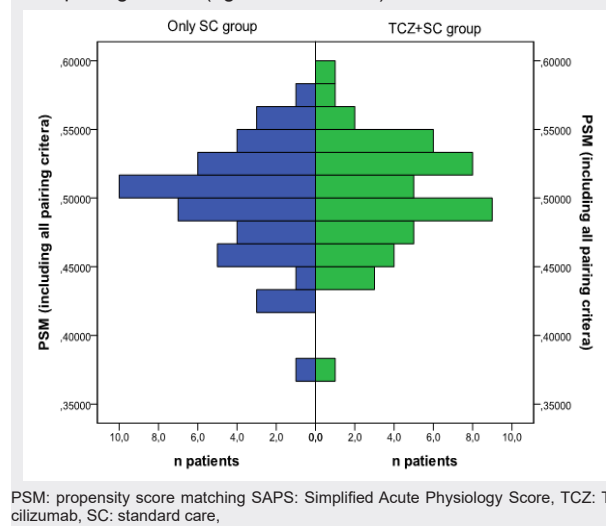
The local ethics committee of the teaching hospital of la Rabta gave the approval for the study design. Regarding the consent, it was not applicable given the retrospective nature of the study. To specify that for the TCZ + SC group, it was their legal parents who obtained TCZ via their own resources after having approved their consent.

RESULTATS

Ninety patients were included by pairing (TCZ + SC group, n=45 versus SC group, n=45), of which 2 pairs corresponded to four postpartum patients.

The matching was considered successful since the PSM exceeded 0.5 in more than 50% of each group for each matching criterion (table 1). By applying the 3 criteria matching, the distribution was symmetric according to the PSM (figure1).

Figure 1. Patients distribution according to the PSM by applying the 3 pairing criteria (age, sex, SAPS II).

PSM: propensity score matching SAPS: Simplified Acute Physiology Score, TCZ: Tocilizumab, SC: standard care,

In addition to the basic comparability of demographic criteria and severity score, obesity, co-morbidities, time to respiratory distress from symptoms onset, RR, respiratory muscle use, initial CRP and P/F ratios, CT scan extension and APP were similar (table 1).

IL-6 was dosed in 32 patients among the TCZ+SC group and it was elevated (level> 7 pg/ml) in all cases with a median value at 84 pg/ml [58-146]. In TCZ+SC group, 26/45 (58%) had a single dose of TCZ and the remaining (n=19) had a double dose. Overall, the median received dose of TCZ was 720 mg [640-800].

Outcomes: 55.5% of SC patients progressed to stage 3 ARDS compared to 31% of TCZ+SC patients (p=0.03). Mortality was identical in both groups and no effect of TCZ was found (49% in each group, p=1). Likewise, no difference was reported in APP failure nor in MV use (p=0.67) nor MV

duration (p=0.4). For the ICU stay, it was more prolonged in TCZ+SC group (16 versus 8 days, p <10-3) (table 1). Biologically, the administration of TCZ induced a significant decrease in CRP (p<10-3), but it did not change the level of IL-6 (p=0,11). ICU-related infections occurred in 18 (40%) among TCZ+SC group comparatively to 15 (33,5%) of SC group, p=0.66 and it was namely represented by hospital or ventilator acquired pneumonia.

Table 1. Clinical characteristics and outcomes in study groups according to the administration or not of Tocilizumab

	TCZ+SC group (n=45)	Only SC group (n=45)	p
Age (years), med [IQR]	52 [41-67]	54 [44-66]	0,49
PSM ≥ 0,5 n (%)	24 (54%)	24 (54%)	
Sex-ratio (M/F)	32/13 (2,46)	32/13 (2,46)	1
PSM ≥ 0,5 n (%)	45 (100)	45 (100)	
SAPS II, med [IQR]	26 [19-30]	26 [20,5-31]	0,16
PSM ≥ 0,5 n (%)	23 (51)	24 (54%)	
Obesity, n (%)	14 (31%)	22 (49%)	0,13
No comorbidities, n (%)	22 (49%)	19 (43%)	0,67
Co morbidites, n (%) :			
Hypertension	11 (24,5)	17 (38)	0,25
Diabetes mellitus	13 (30)	13 (30)	1
Chronic respiratory failure	2 (4,5)	6 (13,5)	0,26
Chronic heart disease	5 (11)	4 (9)	1
Immunodeficiency	4 (9)	0	-
Dysthyroidism	8 (18)	4 (9)	0,35
Time to resp distress from symptomatology onset (days), med [IQR]	11 [8-13]	12 [8,5-14]	0,19
RR (c/mn), med [IQR]	30 [25-36]	31 [25-39]	0,66
Respiratory Muscle use, n (%)	26 (58%)	29 (65%)	0,43
APP, n (%)	41 (91)	39 (87)	0,36
Biology, med [IQR]:			
Baseline P/F ratio	115 [81-143]	101 [78-142]	0,34
CRP (mg/l)			
Baseline	132 [68-160]	145 [82-221]	0,15
Control (post TCZ or day 3)	14 [7-39]	99 [66-175]	**<10^{-3}**
IL-6 (pg/ml) :			
Baseline (32 available)	84 [58-146]		
Post TCZ (10 available)	160 [46-350]		
CT scan extension > 50%, n (%)	23/45 (51)	23/35 (66)	0,21
Outcome :			
APP failure, n (%)	15 (36,5)	17 (43,5%)	0,09
Severity stages of ARDS, n (%):			
Stage 3	14 (31)	25 (55,5)	**0,03**
stage 2	18 (40)	14 (31)	0,06
Stage 1	13 (29)	6 (13,5)	**0,012**
MV use, n (%)	23 (51)	26 (58)	0,67
MV duration, med [IQR]	7 [4-14]	6 [5-10]	0,4
ICU-LOS, med [IQR]	16 [11,5-24,5]	8 [6,5-12]	**<10^{-3}**
Mortality, n (%)	22 (49)	22 (49)	1
ICU-infection, n (%)	18 (40%)	15 (33,5%)	0,66

TCZ: Tocilizumab, SC: standard care, PSM: propensity score matching, RR: respiratory rate, APP: awake prone position, SAPS: Simplified Acute Physiology Score, ARDS: acute respiratory distress syndrom, MV: mechanical ventilation, ICU: intensive care unit, LOS: length of stay.

DISCUSSION

In our paired series, the only benefit of adding tocilizumab to SC in critical forms of Covid-19 was the reduction of progression to severe ARDS; very probably due to its modulating properties on the immune-inflammatory response [3-5]. The considerable reduction of CRP was a marker of that. This last phenomenon was previously highlighted and explained by the fact that IL-6 receptors blockade leads to a sustained suppression of downstream effectors such as CRP [6,7]. In our patients, the effect of CRP regression was observed from day 3 of TCZ administration.

Regarding the clinical effect, we didn't find a beneficial on survival or on MV use but also it did not increase the risk of infections. Differently to what we reported, the systematic review and meta-analysis of Zhao, et al. [8] concluded that Tocilizumab decreased mortality in critically ill patients with OR=0.47; 95% CI [0.36-0.60]; p<0.00001). A reduction in mortality were also found by Malgie, et al. and Lan, et al. of 12% and 7.8% respectively [9,10]. It should be noted that the type of patients studied do not really correspond to critically ill patients apart from the study published in the NEJM [3] and whose patients do not correspond to ICU Tunisian patients (more co morbidities and a longer delay in treatment). Anyway, there was no significant effect on the risk of ICU admission nor on the need for MV in the cohort of Lan, et al. [11]. All these data support the WHO experts recommendation's opting for the use of this molecule rather in patients whose oxygen needs increase rapidly over a short period of time.

The effect of TCZ is mainly shown when the COVID-19 patients exhibited high IL-6 levels before treatment. In the Systematic Review of Antwi-Amoabeng D, et al [10], after TCZ, the values of IL-6 decreased on average to 71.1 (31.9-122.8) pg/mL (p=0.002). Our results didn't support this finding as IL-6 levels varied from 84 pg/ml [58-146] to 160 pg/ml [46-350], p=0,11 comparatively between before versus after TCZ.

Finally, we believe that the attractive benefit of tocilizumab lies in its patho-physiological hypothesis more than in its real clinical impact (survival or MV use). Moreover, in lower income countries such Tunisia, its exorbitant cost (7000 TND per dose!) and its overuse in the era of Covid disrupted the prescriptions in pathologies where it is fully indicated (for example in systemic vasculitis). Tocilizumab should not be considered as a "miracle" treatment for Covid-19. Hyperinflammation with the cytokine storm is not a priori the main pathogenic mechanism of this disease nor the first cause of death. Even more, in critically ill patients, infections and thrombo-embolic complications sometimes overcome. Hence, the benefit of tocilizumab in intensive care patients may be attenuated.

CONCLUSION

Despite the significant reduction of the risk to progress towards severe ARDS by adding tocilizumab to SC in critical Covid-19 forms (probably due to its immune-modulating properties), we failed to demonstrate a benefit neither on survival nor on the MV use.

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