Sarilumab Plus Standard of Care (SOC) Versus SOC For Severe COVID-19 (Escape Study)

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BACKGROUND and AIM

- The pathogenesis of COVID-19 is characterized by a deleterious hyperinflammatory response, associated with the production of a number of proinflammatory cytokines and chemokines, including interleukin (IL)-6[1].
- Different clinical trials have provided some evidences that IL-6 inhibitors use in severe COVID-19 may reduce the duration and/or severity of the disease[2-4].
- Sarilumab is a human monoclonal antibody, which inhibits the binding of IL-6 to its receptor, considered an alternative to tocilizumab in the treatment of severe COVID-19[5]. However, there are less robust evidences for its efficacy[3,4,6-10].

Aim was to evaluate the efficacy of sarilumab, combined with SOC, in patients with severe COVID-19 pneumonia

METHODS

- ✓ **National, multicenter, open-label, phase 3, randomized clinical trial, conducted in five Italian hospitals.**
- ✓ **Study population**: hospitalized patients with SARS-CoV-2 infection and pneumonia, in severe or critical conditions and with evidence of hyperinflammation; mechanically ventilated patients were excluded; follow up period of 30 days.
- ✓ **2:1 randomization** to receive sarilumab 400 mg, repeatable after 12 hours, plus SOC (**arm A**) or to continue SOC (**arm B**), stratified by severity of illness (PaO_2/FiO_2 ≥200 mmHg and PaO_2/FiO_2 <200 mmHg or the presence of noninvasive ventilation [NIV]).
- ✓ **Primary endpoint**: time to clinical improvement of 2 points on a 7-point category ordinal scale[§] evaluated
  - in the modified Intention to treat (mITT) population*,
  - after stratifying according to baseline disease severity (PaO_2/FiO_2 ratio < or ≥ 200 mmHg);
  - after stratifying according to inflammatory parameters[#];
- ✓ **Key secondary endpoints**:
  - time from treatment initiation to death;
  - evaluation of adverse events, serious (SAEs) and not (AEs);
  - evaluation of secondary bacterial or fungal infections;
- ✓ **Statistics**: *Chi square test* to compare proportions between arms, *Cox regression,* stratified by clinical center, to estimate the hazard risk (HR) of primary endpoint. *Interaction test* was also performed.

***mITT population** included all the patients who had undergone randomization and received a dose of sarilumab or continued SOC therapy [§]**1.**not hospitalized, with resumption of normal activities; **2.**not hospitalized, but unable to resume normal activities; **3.**hospitalized, not requiring supplemental oxygen; **4.**hospitalized, requiring supplemental oxygen; **5.**hospitalized, requiring NIV; **6.**hospitalized, requiring ECMO, invasive mechanical ventilation, or both; **7.**death. [#]Baseline CRP < or ≥7 mg/dL and lymphocytes < or ≥870/mmc.

See supplemental materials for inclusion/exclusion criteria

EFFICACY ANALYSIS

Figure 1a-c. Kaplan Meier survival curves estimating the cumulative proportion of patients who experienced the primary endpoint at day 30, in the mITT population (1a) and after stratifying for inflammatory parameters (baseline CRP <7 mg/dL [1b] and lymphocytes count <870/mmc [1c]).* Interaction tests between strata are shown.*

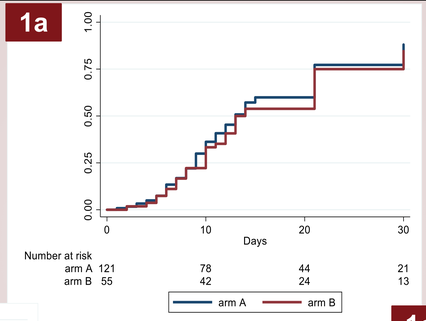
**No differences for the other two strata (CRP >7 mg/dL and lymphocytes count >870/mmc).*

1a

arm A 88.0% (95% CI 76.7-95.5)
arm B 78.9% (95% CI 62.7-91.4)

HR 1.53 (95% CI 0.90-2.62); log-rank *p*=0.049

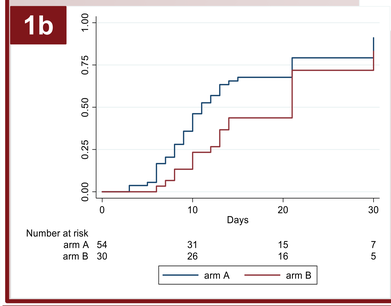
***p* at interaction test = 0.09**



1b

arm A 88.0% (95% CI 81-94)
arm B 85.0% (95% CI 74-93)

HR 1.08 (95% CI 0.76-1.55); log-rank *p*=0.65

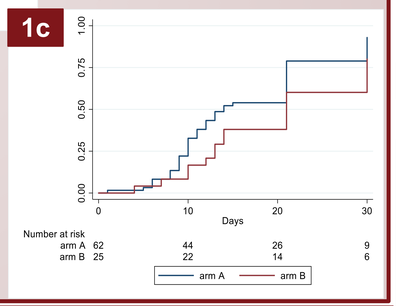


1c

arm A 88.0% (95% CI 76.7-95.5)
arm B 78.9% (95% CI 62.7-91.4)

HR 1.48 (95% CI 0.84-2.59); log-rank *p*=0.058

***p* at interaction test = 0.05**



DESCRIPTIVE ANALYSIS

Table 1. Patients' characteristics at baseline.

TABLE 1	Arm A (sarilumb group) N=121	Arm B (SOC group) N=55	*p-value*
Gender, male, n (%)	97 (80.2%)	37 (67.3)	0.063
Age, years, median (IQR)	61 (53-70)	59 (52-72)	0.718
Ethnic group, caucasian, n (%)	113 (93.4%)	52 (94.6%)	0.769
Comorbidities			
Chronic cardiac disease, n (%)	5 (4.1%)	2 (3.6%)	0.619
Chronic pulmonary disease, n (%)	36 (29.8%)	15 (27.3%)	0.977
Diabetes, n (%)	4 (3.3%)	1 (1.8%)	0.501
Active malignant neoplasm, n (%)	0	0	-
Chronic kidney disease, n (%)	0	1 (1.8%)	-
Treatment			
Sarilumab doses			
1 dose, n (%)	63 (52.1%)	-	
2 doses, n (%)	58 (47.9%)	-	
Corticosteroids, n (%)	44 (36.4%)	26 (47.3%)	0.170
Remdesivir, n (%)	22 (18.2%)	8 (14.6%)	0.552
Median laboratory parameters (IQR)			
CRP, mg/dl	7.0 (4.3-12.3)	6.1 (3.3-9.8)	0.075
Lymphocytes, x1000/mm³	0.85 (0.62-1.24)	0.89 (0.62-1.23)	0.948
Ferritin, pg/ml	975 (493-1485)	768 (486-1203)	0.191
D-dimer, ng/ml	564 (365-919)	640 (358-994)	0.667
LDH, IU/l	356 (272-418)	334 (271-421)	0.775
Platelet, x1000/mmc	229 (170-283)	232 (176-311)	0.443
Fibrinogen, median (IQR)	587 (479-703)	563 (452-640)	0.149
PaO_2/FiO_2, mmHg, median (IQR)	212 (148-280)	197 (160-264)	0.447
Clinical status on ordinal scale[§], median (IQR)	4 (4-5)	4 (4-5)	0.712

- ✓ The main demographic, clinical, therapeutic and laboratory characteristics were equally distributed in the two groups.
- ✓ Study participants had a high median age, with mainly pulmonary comorbidity.
- ✓ A similar proportion of patients received treatment with corticosteroids and/or remedesivir.
- ✓ Two doses of sarilumab were prescribed in about half the population.

***Abbreviations**: CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; n, number; PaO_2/FiO_2, partial pressure of arterial oxygen/fraction of inspired oxygen.*

SAFETY ANALYSIS

Table 2. AEs, SAEs and secondary infections. *Abbreviations: MDR, multi drug resistant pathogens; SSTIs, skin and soft tissue infections.*

TABLE 2	Arm A (sarilumab group) N=121, n (%)	Arm B (SOC group) N=55, n (%)	*p-value*
Adverse events	32%	23%	0.195
Serious adverse events	18%	11%	0.244
Bacterial infections			
Pneumonia	6 (5%)	1 (1.8%)	0.323
Blood stream infections	5 (4.1%)	4 (7.3%)	0.381
Urinary tract infection	4 (3.3%)	1 (1.8%)	0.582
SSTIs	1 (0.8%)	0	0.499
MDR infection	4 (28.6%)	3 (75.0%)	0.093
Fungal infections			
Candidemia	1 (0.8%)	1 (1.8%)	0.565
> 1 infection	3 (2.5%)	3 (5.4%)	0.313
Secondary infection according to Sarilumab doses*,		- ***p=0.015**	
one dose	3/63 (4.8%)	-	
two doses	11/58 (19.0%)	-	0.323

See supplemental materials for other results

CONCLUSIONS

- ➢ In this randomized, multicenter, open-label clinical trial, intravenous sarilumab added to SOC did not show higher efficacy compared to SOC in patients with severe COVID-19.
- ➢ Some benefits were shown in those participants treated at an early stage of the disease with lower inflammatory burden.
- ➢ The low rate of concomitant corticosteroid use among the study participants, could partially explain our results, considering that in two of the larger trials on IL-6 inhibitors [2,3], the clinical benefit of IL-6 blockade was clear when administered in combination with dexamethasone.
- ➢ Sarilumab treatment confirmed to be safe in terms of AEs, but secondary infections may be a concern among patients receiving two doses.
- ➢ Further trials are needed to better identify targeted subgroups of patients with COVID-19 who are likely to benefit from this treatment and the optimal timing for sarilumab administration to maximize the efficacy.

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