Abstract 1708 – Safety of IL-17A blockade with secukinumab in Covid-19 hospitalized patients – interim data from the BISHOP study.

Gustavo Resende[1], Amanda Medeiros[2], Alessandra Silva[2], Antonio de Sá[2], Argenil de Oliveira[2], Denise Sousa[2], Henrique Guimarães[2], Isabella Gomes[2], Renato Santana[3], Ricardo Lage[1], Samara Lobê[2], Roberto Tunala[4], Francisco Forestiero[4], Mauro Teixeira[5]

[1] Hospital das Clínicas – UFMG/EBSERH, [2] Hospital Risoleta Tolentino Neves, [3] Departamento de Genética, Ecologia e Evolução – ICB/UFMG, [4] Novartis Brasil, [5] Departamento de Bioquímica e Imunologia – ICB/UFMG

Background

The new coronavirus (SARS-CoV-2) pandemic has spread across the planet and threatens all health systems globally. Patients with severe forms of COVID-19, who progress to acute respiratory distress syndrome (ARDS), seem to have a combination of deficient antiviral immunity (type 1 immune response) with hyperinflammation. IL-17A is an inflammatory cytokine with a major role in immune protection against extracellular pathogens (signature of type 3 immune response). It is a potent neutrophil attractor and activator through chemokines such as CXCL8 and growth factors such as G-CSF. There were already some previous attempts to block IL-17A in animal models of viral infections, but to our knowledge, there is no study published of IL-17A inhibition in COVID-19. We hypothesized that the use of secukinumab (SEK), a monoclonal antibody anti-IL17A, could prevent or mitigate the hyper inflammation and its deleterious consequences in severe COVID-19 patients.

Methods

The BISHOP study is an ongoing open-label, single-center, phase 2, controlled clinical trial, which is recruiting since September 2020. Adult patients with SARS-CoV-2 infection confirmed by RT-PCR admitted to Hospital Risoleta Tolentino Neves in severe acute respiratory syndrome according to the Brazilian Ministry of Health definition were randomized 1:1 to receive a dose of 300mg of SEK subcutaneously at D0 (group A) in addition to standard of care (SoC) or follow the SoC alone (group B). According to attending medical team judgment, a second 300mg dose of SEK could be administered at D7 for those included in group A if the study's inclusion and exclusion criteria remain applicable. The primary endpoint is the ventilator-free days in 28 days (VFD28). Here, we present the first 20 patients' interim data (40% of the expected sample) interested in secukinumab's safety profile in this population. This research was supported by Novartis Brazil. Novartis Brazil also provided expert input in developing the project as drug supply, data management, and monitoring.

Results

This present analysis uses the data from the first ten included patients in each group. The number of serious adverse events (SAE) in groups A and B were 11 and 5, with an incidence rate per 100 patients-day of 3.9 and 2.0. Pulmonary thromboembolism occurred in three patients from group B and one from group A. Septic shock, defined as hemodynamic instability and the identification of an infectious focus by culture, occurred in two patients from group A and one from group B. Only one patient discontinued the study (group B) due to intolerance to consecutive nasopharyngeal swab. There was one death in each group, both due to septic shock secondary to ventilator-associated pneumonia (VAP). No fungal infections nor injection site reactions were observed. The viral RNA was quantified on day zero (D0) and day five (D5) by nasopharyngeal swab RT-PCR. The remaining viral load on D5 compared with D0 (2-ΔΔCT method) designated the viral clearance. It was remarkably similar between the two groups (0.10 in group A and 0.07 in group B), as shown in figure 1.

Group	SoC + Secukinumab			SoC		
	median	IQR		median	IQR	
Age (years)	61	48	68	49	37	62
Sex (male)	60%			80%		
No of comorbidities	1	1	2.3	1	1	2
Symptoms (days)	11	10	13	11	9	11
NLR	3.89	4.54	4.18	4.94	5.25	6.41
PaO2/FiO2 ratio	213	166	344	179	170	338
Ferritin (ng/mL)	955	604	1470	1287	880	1709
Troponin (ng/mL)	5.0	2.0	14.2	5.5	2.1	11.8
D-dimer (mcg/mL)	0.9	0.7	3.1	1.0	0.5	5.9
CRP (mg/L)	39	26	93	66	30	128
SOFA score	2.5	1.3	3.0	3.0	1.0	3.0

Table 1: Baseline and disease characteristics of patients. SoC: Standard of care; IQR: Interquartile range; NLR: Neutrophils/Lymphocytes ratio; PaO2: Partial pressure of oxygen; FiO2: Fraction of inspired oxygen; CRP: C-Reactive Protein; SOFA: Sequential Organ Failure Assessment.

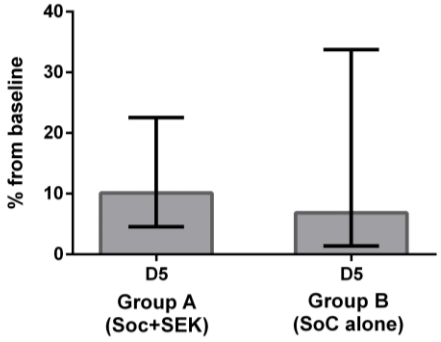

Figure 1 – SARS-CoV2 clearance in upper airways. The percentage of viral RNA on D5 compared to D0 was 10.1% (95%CI 4.6-22.6) in group A and 6.7% (95%CI 1.4-33.7) in group B. SoC: standard of care; SEK: secukinumab

Conclusions

This preliminary analysis suggests that the association of SEK to SoC in patients with severe COVID-19 has a good safety profile. No significant difference between groups was observed regarding serious adverse events, pulmonary thromboembolism, septic shock, and deaths. The IL-17A blockade also does not seem to interfere with the viral clearance in the upper airways.