COVID-19 Pathophysiology leading to the drugs to be used

CO0001

MAVRILIMUMAB IMPROVES OUTCOMES IN SEVERE COVID-19 PNEUMONIA AND SYSTEMIC HYPER-INFLAMMATION

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Background: Patients with severe COVID-19 pneumonia and hyperinflammation face increased mortality. There is an urgent need for effective treatments to reduce the burden of the COVID-19 pandemic.

Objectives: Our protocol aimed at evaluating the potential improvement in clinical outcomes with mavrilimumab, an anti-Granulocyte/Macrophage Colony-Stimulating Factor Receptor alpha (GM-CSFRα) monoclonal antibody, in patients with COVID-19 pneumonia and systemic hyper-inflammation.

Methods: Single-center, open-label, single active arm intervention; Adult patients with severe COVID-19 pneumonia (as evaluated by CT scanning), hypoxia (PaO₂:FiO₂ ratio ≤ 300 mmHg), and systemic hyper-inflammation (increased C-reactive protein [CRP] ≥ 100 mg/mL and/or ferritin ≥ 900 µg/L, increased lactate dehydrogenase [LDH]) received a single intravenous dose of mavrilimumab added to standard of care; follow-up 28 days. Main outcomes measure was time to clinical improvement (reduction ≥ 2 categories on the 7-point WHO clinical status scale, 1=discharge, 7=death); others included time to discharge from hospital; % of pts achieving a clinical improvement; survival; mechanical-ventilation free survival; time to fever resolution; CRP; PaO₂:FiO₂ ratio.

Results: A mavrilimumab group (n=13 COVID-19 patients, non-mechanically ventilated, median age 57 [IQR, 52-58], males 12 [92%], febrile 11 [85%]; PaO₂:FiO₂ 195.5[166.7-215.0]) was compared to a cohort of 26 contemporaneous patients with similar baseline characteristics. Death occurred in 0% (n=0/13) of mavrilimumab recipients and 27% (n=7/26) of comparison-group patients (log rank p=0.046) during the 28-day follow-up. 100% (n=13) of mavrilimumab recipients and 65% (n=17) of comparison-group patients achieved clinical improvement (p=0.018) at Day 28, with earlier improvement (median 8.0 [IQR, 5.0-11.0] days vs 18.5 [11.0-NE] days) (p<0.001) in mavrilimumab recipients. Fever had resolved in 91% (n=10/11 febrile patients) of mavrilimumab recipients by Day 14, compared to 61% (n=11/18 febrile) of patients in the comparison group (p=0.110); fever resolution was faster in mavrilimumab recipients versus controls (median 1.0 [IQR, 1.0-2.0] day vs 7.0 [3.0 - NE] days, respectively, p=0.009). Mavrilimumab was well tolerated in all patients.

Conclusion: Patients with severe COVID-19 pneumonia and systemic hyper-inflammation who received treatment with mavrilimumab had better clinical outcomes compared to patients receiving routine care. Mavrilimumab was well-tolerated. Randomized controlled trials are warranted to confirm our findings.

References:

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CO0002

LOSS OF SELF-TOLERANCE IN SARS-COV-2 INFECTION: IMMUNOLOGICAL ASSESSMENT OF A CONVALESCENT COHORT

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Background: Some infectious agents may act as inducers of autoimmune conditions¹. Despite SARS-CoV-2 infection can induce autoimmune phenomena in infected people², individual risk factors or underlining mechanisms leading to loss of immunological tolerance are still unknown.

Objectives: To assess the rate of development of autoantibodies in convalescent SARS-CoV-2 patients and their relation on infection clinical course and disease parameters.

Methods: One-hundred and nine convalescent SARS-CoV-2 patients were studied and underwent multidisciplinary assessment in a Day Hospital clinical setting. For each patient, demographic, clinical and immunological data were collected and, at study entry, autoimmune profile [antinuclear antibodies (ANAs), antibodies reacting with extractable nuclear antigens (anti-ENA), antineutrophil cytoplasmic antibodies (ANCAs), Lupus anticoagulant (LA), anticardiolipin antibodies (aCL) IgM and IgG, anti-β2 glycoprotein I (anti-β2GPI) IgM and IgG] was assessed by Fluorescent immunoassay. Moreover, IL-6 plasma levels were assessed by ELISA (ELLA).

Results: After a median time from hospitalization for SARS-CoV-2 infection of 53.3 ± 0.9 days, 55(50.5%) SARS-CoV-2 convalescent patients showed the positivity (AB^{pos}) of at least one autoantibody. In particular, 31(28.4%) were positive for LA, 11(10.1%) for IgM-RF, 8(7.3%) for ANA and 6(5.5%) for IgG-aCL whilst less than 2% showed other autoantibody positivities (IgM-aCL, IgG-anti-β2GPI, ENA, ACPA, c-ANCA, Scl70 and RNP). Analyzing the patient-related characteristics associated with the development of autoimmunity, convalescent male patients were more likely characterized by the development of antiphospholipid antibodies (aPL) (37.3%) than female (16.7%; p=0.02). Considering the disease-related characteristics, convalescent SARS-CoV-2 patients who experienced severe pneumonia (i.e., oxygen support need) during hospitalization, more likely received IL-6R-inhibitor administration (47.3%) and developed more than one autoantibody (87.5%) (aPL + another AB) than convalescent SARS-CoV-2 patients who did not need oxygen support ([12.5%; p=0.02] (OR95%IC: 9.5(1.4-109.1)) or IL-6R-inhibitor (1.9%; p<0.001). Finally, assessing cytokines plasma levels in convalescent SARS-CoV-2 patients stratified based on the development of autoantibodies we found that, despite a significant reduction of IL-6 plasma levels from hospitalization, convalescent SARS-CoV-2 patients who developed autoantibody positivity had higher IL-6 plasma levels (8.5 ± 2.5 pg/ml) than convalescent SARS-CoV-2 AB^{neg} patients (5.6 ± 1.5 pg/ml; p=0.07), mostly if considered autoantibodies other than aPL (15.4 ± 7.7 pg/ml)(p=0.01).

Conclusion: Loss of self-tolerance is a common phenomenon in the medium-term follow-up of SARS-CoV-2 convalescent patients whose occurrence is dependent by a severe disease course and by an aberrant host inflammatory response. Long-term follow-up will reveal AB persistency and their clinical impact.

References:

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CO0005

C-C CHEMOKINE RECEPTOR TYPE 5 AND ITS LIGANDS CCL4, 8 AND 11 CAN LINK COVID-19, RHEUMATOID ARTHRITIS AND HYDROXYCHLOROQUINE

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Background: Coronavirus disease (COVID-19) caused by SARS-CoV2 represents an unprecedented global public health concern with a particular burden on patients with chronic diseases and those on immune-modulating drugs. It is especially worrisome to patients with rheumatoid arthritis (RA) who are on immune suppression regimens[1]. On the other side, many reports showed and recommended the use of some Disease-Modifying Drugs commonly used to treat rheumatic diseases like hydroxychloroquine. However, the general understanding of COVID-19 characteristics in this population and the mechanism of action of these drugs in COVID-19 is still unknown[2].