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.

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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.

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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].

Objectives: Explore publicly available transcriptomic dataset of patients infected with SARS-COV2 compared to uninfected to identify differentially expressed genes (DEGs) related to the immune system that might be pathogenic in RA synovium. Then explore the effect of Disease-Modifying Drugs on their local expression that might give hints about their possible mechanism of action.

Methods: RNAseq dataset (GSE147507) were retrieved using the Gene Expression Omnibus (GEO) and used to identify DEGs between infected and uninfected lung samples using BioJupies tools [3]. The DEGs were explored for common pathways using Metascape online tool (<http://metascape.org>) [10], as shown in figure (1). The chemokines genes were filtered out, and their common receptor (CCR5) was identified. The immune cells that express a higher level of the identified receptor were explored using DICE project tool (<https://dice-database.org/>). The expression of CCR5 was searched in a microarray dataset (GSE77298) of synovial biopsies of RA and healthy controls. RNAseq dataset (GSE97165) of synovial biopsies taken from 19 early RA patients at baseline and after six months of Triple Disease-Modifying Anti-rheumatic drugs (tDMARD; methotrexate, sulfasalazine, and hydroxychloroquine) treatment.

Results: 84 DEGs were identified between uninfected and COVID-19 infected lung samples. These DEGs were enriched in pathways specific to (response to the virus, response to interferon, leukocyte activation, and chemotaxis). Interestingly, SARS-COV-2 infected lungs express more CCL4, CCL8, and CCL11; the three ligands shared the same receptor, which is CCR5. Top immune cells that express CCR5 were CD4 T memory T reg cells, Th17, Th1, and monocytes. CCR5 was significantly upregulated in RA compared to healthy controls synovium ($p=0.04$) and was dramatically downregulated after six months of tDMARD treatment ($p=0.004$), as shown in figure (2).

Conclusion: Using publicly available transcriptomic datasets properly highlighted the possible beneficiary effect of DMARDs in patients with COVID-19, which can block CCR5 rich immune cells recruitment.

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Figure 1. Flowchart of transcriptomic analysis

Figure 2. (A) Top immune cells that express CCR5 (B) CCR5 expression in synovial biopsies of RA and control (C) CCR5 expression at baseline and after 6 months of tDMARD treatment.

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Talk about the consequences of COVID-19 on RMDs

CO0003 TREATMENT WITH BIOLOGICAL THERAPIES AND RISK OF BEING ADMITTED TO THE HOSPITAL FOR COVID19 INFECTION

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Objectives: To analyze the risk of admission for COVID19 infection and outcome of patients treated with bDMARD or tsDMARD from our biologic therapy center, to compare with all patients admitted for COVID-19 infection in our hospital.

Methods: Records of the patients from our center admitted for COVID-19 infection between March 8 and May 8, 2020 were analyzed retrospectively. Age, gender, and outcome of all patients admitted for COVID19 infection to our hospital on the same dates were collected. Chi-square, Student's t and Man-Whitney U tests were used for comparisons when appropriate.

Results: 1,668 patients with inflammatory diseases treated with bDMARD or tsDMARD were included. Median age 53.0 years (range 17-91), 52.4% women. Diagnoses and DMARD distribution are shown in tables 1 and 2. 19/1668 (1.1%; 6.8 patient-years) were admitted for severe COVID19 infection. Mortality ratio: 4/19 (21.1%). Median age of the admitted patients was higher: 61.0y (SD 14.2) vs 53.0y (SD 15.0); $p < 0.009$. Median age of deceased patients was also higher 69.5y (SD 20.3) vs 53.0y (SD 15.0); p : NS. Female gender had a worse prognosis trend: 52.4% of all group, 68.4% of those hospitalized, 75.0% of those who died. Females had a higher median age than men: 55.0y (SD 14.9) vs. 50.0y (SD 14.9); $p < 0.001$.

When comparing patients treated with DMARD admitted for COVID19 infection with all patients hospitalized for the same reason (4,601 patients), no differences were found neither in age (61.0y [SD 14.2] vs 58.3y [SD 18.1]; NS) nor gender (female: 68.4% vs 54.7%; NS). However, DMARD group seemed to have higher mortality: 4/19 (21.1%) vs 551/4601 (12.0%); p : NS, at a younger age: 69.5y (SD 20.3) vs 82.4 (SD 11.4); p : NS.