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Tocilizumab, blood cells, and mild COVID-19: delayed vascular protection by interleukin blockade?

The ongoing COVID-19 pandemicand lack of proven therapeutic strategies lead to testing and regulatory approval for various existing agents, including array of monoclonal antibodies. Tocilizumab (Actemra®, Genentech; distributed in Russia by Roche) binds to both soluble and membrane-bound intraleukin-6 receptors inhibiting this pleiotropic proinflammatory cytokine.[1] The drug is currently approved for various vascular indications, including rheumatoid arthritis. The data on tocilizumab efficacy for COVID-19 are plenty, but inconclusive. Eight randomized clinical trials of tocilizumab for treating patients with COVID-19 have reported heterogeneous results. Although four of them achieved their primary endpoint, improved 28-day survival was demonstrated only in the two largest studies and those with the highest mortality (RECOVERY and REMAP-CAP).[2] Indeed, a strong trend towards reduced COVID-19 mortality (16.3% vs. 24.1%) after tocilizumab treatment may be important. Lately, COVID-19 is under scope for triggering and/or causing disturbances in cell–endothelial crosstalk. Obviously, the critical cases of COVID-19 are

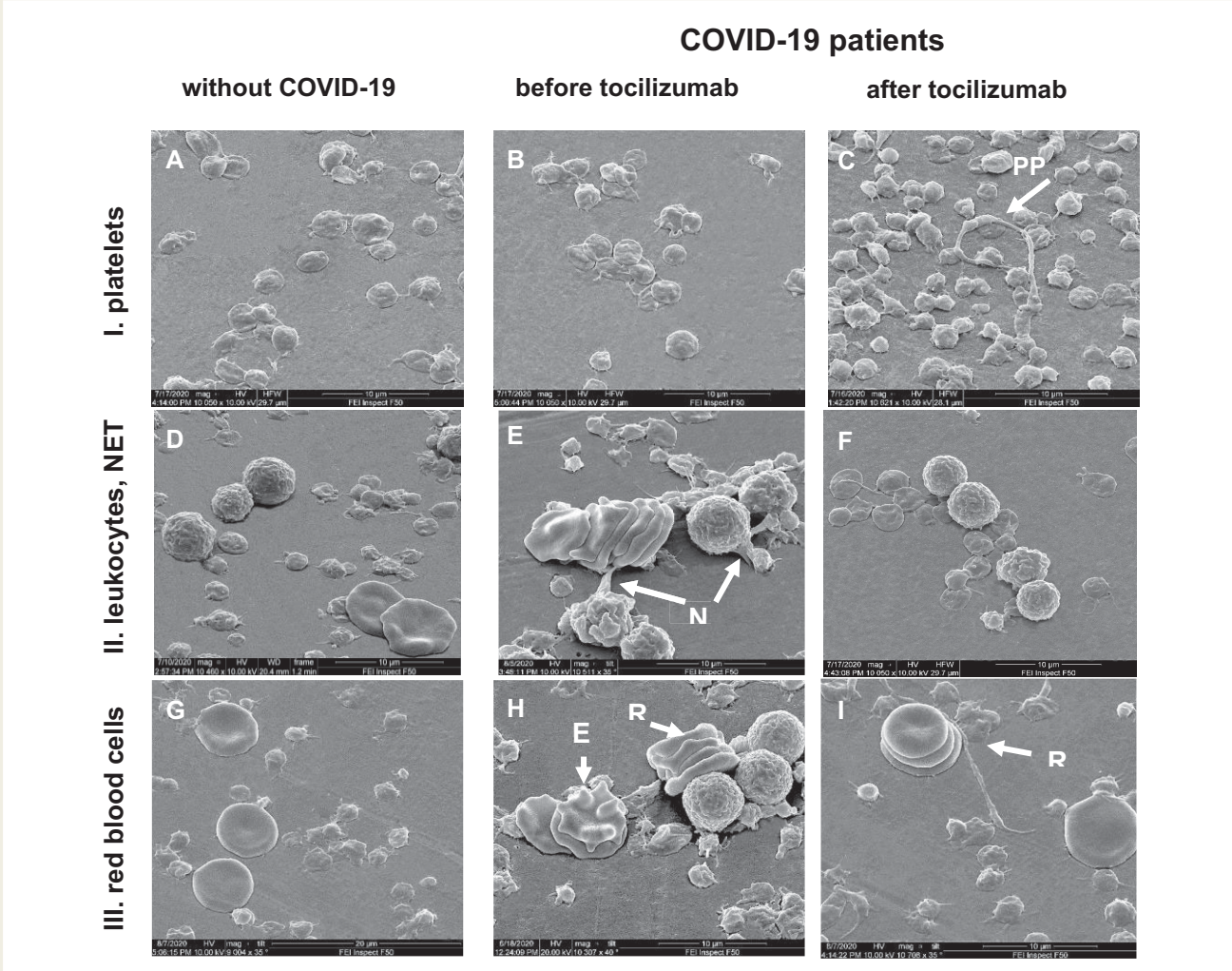

Figure 1 I. Platelets. Mostly discs in controls (*A*); less quantity, activation, sphere transformation, at COVID-19 admission (*B*); increased production and pseudopodia generation (PP arrow) due to enhanced megakaryocytopoiesis following tocilizumab treatment at discharge (*C*). II. Leukocytes. No clusters or neutrophil extracellular traps in controls (*D*); massive traps in COVID admission samples exhibited by N arrows (*E*); less or no traps after tocilizumab treatment (*F*). III. Red blood cells. Biconcave shape with no rouleaux formation in controls (*G*); transformation of erythrocytes into echinocytes (E arrow) and formation of circulated erythrocyte rouleaux (R arrow) at COVID-19 admission (*H*); less echinocytes in numbers and piles (R arrow) (*I*) after tocilizumab treatment. Magnification ×10 000 for all cell images.

characterized with pronounced coagulopathy and endothelial dysfunction.[3–5] However, the validity of such association is based mostly on sporadic random clinical observations or autopsy, while precise cellular data in survivors, or the impact of anti-inflammatory agents on blood cell preservation and vascular protection, are lacking. We here utilized scanning electron microscopy assessing impact of tocilizumab on phenotype and interactions between erythrocytes, leukocytes, and platelets in hospitalized COVID-19 patients. Patients ($n = 9$) with PCR-confirmed COVID-19 diagnosis were admitted to the hospital from 25 May to 22 July 2020 and included in this single-centre prospective observational study. The details are outlined elsewhere.[6] Admission and discharge venous blood samples were collected for electron microscopy. The demographics and comorbidities in the COVID-19 patients match well, but not ideally probably due to small sample size. Tocilizumab 400 mg single dose subcutaneously ($n = 4$), or next day repeated administration for the total of 800 mg ($n = 5$), was compared with COVID-negative matched control patients ($n = 32$). During the hospital stay, all patients survived, and no patient was referred to ICU or required mechanical ventilation. The typical differences in blood cell structures before and after tocilizumab treatment are exhibited in *Figure 1*.

We are extremely limited in making any assumptions due to the small sample size, and different tocilizumab doses and treatment duration. Moreover, our COVID-negative controls were not ideally matched. However, there are few important advances raised by the index preliminary report. First, the interleukin blockade unquestionably improves erythrocyte membrane permeability, reducing echinocytosis and sludge formation. It seems that tocilizumab decreases nuclear net neutrophil construction without impacting platelet–leucocyte crosstalk. The drug definitely does not increase platelet activation, but rather stimulates their production enhancing excess young platelet circulation. In lay terms, we found no evidence that tocilizumab hurts any cellular biomarkers in COVID-positive patients. These effects were mild but either neutral or positive suggesting recovery. Second, discharge samples from COVID survivors revealed ongoing blood cell damage potentially requiring delayed protection far beyond hospitalization. Finally, long-term controlled outcome-driven trials with hard endpoints are urgently needed for exploring optimal antithrombotic and vascular protection strategies by targeting numerous inflammatory markers in general and interleukin in particular.

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