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Colchicine in COVID-19 – The Colcorona Trial

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Colcorona was a multicenter, international study promoted by the Montreal Heart Institute, Canada, whose main objective was to test the effects of colchicine in non-hospitalized patients with COVID-19 [1]. So far, the majority of studies addressed hospitalized patients which is understandable since mortality occurs mainly among those individuals. The Colcorona, however, focused specifically in non-hospitalized patients because preventing hospitalization and death are important therapeutic targets. Inclusion criteria were age ≥ 40 years, one or more risk factors, including arterial hypertension, heart failure, diabetes, coronary disease, fever, age ≥ 70 years or obesity. Diagnosis was based on positive PCR from nasal swab. Given restriction in PCR swab at beginning of the pandemic, a minority of patients were enrolled based on clinical criteria. The initial intention was to enroll 6,000 patients in a randomized, double-blind approach, comparing colchicine – 0.5 mg twice daily for the initial 3 days, followed by 0.5 mg daily for the following 27 days vs. a placebo. However, the study was terminated with 75% of enrollment for logistical reasons; thus 4,488 patients were included of whom 2,235 received colchicine and 2,253 the placebo [1].

The rationale for the study was to investigate whether preventing the "cytokine storm" that occurs in the early phase of SARS-COVID infection would reduce the combined primary endpoint of death and hospitalization. This "cytokine storm" plays a decisive role in COVID-19, causing excessive liberation of interleukin-6, Interleukin-1 and TNFα among other inflammatory cytokines which are reflected in increased plasma reactive C protein and leukocytosis. Cytokines also profoundly affects platelets and coagulation/fibrinolytic systems causing thrombosis, bleeding and severe limb ischemia. Another consequence is widespread endothelial dysfunction which contributes to respiratory failure, renal, neurological both central and peripheral, cardiac and digestive disturbances that characterize the course of the disease in individuals with severe forms [2].

Colchicine was chosen because it is a well-known anti-inflammatory drug with proven efficacy as an anti-rheumatic medication and also in treating chronic pericarditis. Colchicine has multiple anti-inflammatories and antiproliferative actions including reduction in reactive oxygen species production, impeding activation of NLRP3 inflammasome and consequently reducing IL-1β and the formation of other cytokines; colchicine specifically blocks ROS induction of NFKβ pathway and TNFα formation. Importantly, it acts upon neutrophils, reducing chemotaxis, adhesion and mobilization. Most significantly, however, colchicine blocks polymerization of microtubules by rupturing tubulin and forming the tubulin–colchicine complex; as previously observed microtubules are essential for cell proliferation. Their side-effects are well known, especially gastro-intestinal such as diarrhea and intestinal pain, which promptly subside upon drug suspension [3].

In the Colcorona trial, the primary combined endpoint of death and hospitalization was reduced from 131 (5.8%) in the placebo group to 104 (4.7%) in the colchicine group but did not reach statistical significance (p=0.08). However, among the 4,159 patients with positive nasal PCR for COVID-19, at least 1 risk factor such as heart failure, diabetes, obesity or hypertension the composite endpoint was reduced significantly from 126 (6.0%) in the placebo group to 96 (4.6%) in the colchicine group (p=0.042). This subgroup had been pre-specified in the statistical analysis. In addition, patients with a history of diabetes, ≥ 72 years of age and male obtained greater improvement than those without these conditions. On the other hand, gastro-intestinal effects, especially diarrhea, were more common among colchicine users. Also, pulmonary embolism was more frequent among colchicine. While diarrhea is a

relatively common side-effect, pulmonary embolism was an unexpected and unexplained finding.

The authors concluded that in selected non-hospitalized patients with proven COVID-19 infection, colchicine may be a viable alternative to reduce the combined endpoint of hospitalization/death.

Different studies have focused on the issue of combating inflammation in COVID-19 among hospitalized patients. In the UK "RECOVERY" study, colchicine was not beneficial in hospitalized patients with COVID-19 who had already been treated with corticosteroids among other drugs [4]. On the other hand, Tofacitinib, a Janus kinase inhibitor, was tested on COVID-19 hospitalized patients with pneumonia and led to a lower risk of death or the need for mechanical ventilation at 28 days compared to placebo, in the STOP-COVID trial in Brazil [5]. Tocilizumab, an anti-interleukin-6 receptor antibody, when given to hospitalized patients with pneumonia not receiving mechanical ventilation reduced the likehood of progression to the composite endpoint of death/mechanical ventilation [6] compared to placebo.

Also, intravenous Remdesivir reduced recovery time in hospitalized patients with Covid-19 and lower respiratory tract infection in the ACTT-1 Trial [7]. Similarly, Cavalli et al. also [8] reported that the interleukin-1 blockade with high-dose anakinra was safe and effective in a retrospective study.

Corticosteroids have been effective in reducing the severity of respiratory involvement, but only in hospitalized patients [9] and today is a cornerstone measure in COVID-19 treatment.

The most appealing aspect of colchicine is the long experience of its use in other inflammatory diseases, such as rheumatic conditions; Mediterranean fever, chronic pericarditis and in CAD patients after myocardial infarction. Further, the Grecco study [10] showed clinical benefits in hospitalized patients with COVID-19 in a small group of patients. Colchicine is also widely available throughout the world and inexpensive; the latter aspect is especially significant for low-income countries where vaccination is more limited. Resurgence of cases due to decreasing efficiency of vaccines over time and the increasing number of cases due to delta variant of COVID, highlights the relevance of protecting patients from hospital admission. Also, a considerable number of persons refuse vaccination everywhere; in some countries they presently respond for most hospitalizations.

Finally, considering the overload of intensive care units during this pandemic, any intervention that could prevent or reduce hospitalization would be more than welcome. Although Colcorona did not offer definite answers to the questions above, it raises some valuable insights that justify further investigations.

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