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63rd ASH Annual Meeting Abstracts

POSTER ABSTRACTS

803. EMERGING DIAGNOSTIC TOOLS AND TECHNIQUES

Association between Insufficient Interleukin-6 (IL-6) Inhibition and Worsening Outcomes in COVID-19 and Idiopathic Multicentric Castlemans Disease (iMCD), and a Mathematical Model to Predict Optimal Dosing to Completely Block IL-6 Activity

Jean-Francois Rossi^{1,2}, Hao-Chun Chiang³, Zhao-Yang Lu⁴, Kalle Levon³, Frits van Rhee⁵, Karan Kanhai⁶, David C Fajgenbaum^{7,8}, Bernard Klein⁹

¹ Faculté de Médecine Montpellier, Université de Montpellier, Montpellier, France

² Hématologie-Immunothérapie, Institut du Cancer Avignon-Provence, Sainte Catherine, France

³ Department of Chemical and Biomolecular Engineering, NYU Tandon School of Engineering, NY, NY

⁴ Unité de Thérapie Cellulaire, CHU Montpellier Saint-Eloi, Montpellier, France

⁵ Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR

⁶ Medical Affairs, EUSA Pharma, Hemel Hempstead, United Kingdom

⁷ Center for Cytokine Storm Treatment & Laboratory, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁸ Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁹ Faculté de Médecine Montpellier, Université de Montpellier, Montpellier, France

Abstract Dysregulated inflammatory responses are characterized by inappropriate levels of inflammatory markers, speed of generation, degree, and major site of production, such as a vital organ. COVID-19 severity and mortality are strongly associated with interleukin (IL)-6 levels. High IL-6 levels are also observed in idiopathic Multicentric Castlemans Disease (iMCD). Previously, we developed the first anti-IL-6 monoclonal antibody (mAb) treatments and showed that C-reactive protein (CRP) production could be fully controlled by IL-6 in humans. Using mathematical modeling, with CRP as an IL-6 surrogate marker, we predicted the ability of an anti-IL-6 mAb to block plasma IL-6 activity and showed IL-6 inhibition was dependent on the extent of whole-body IL-6 production. We postulate that in patients (pts) in whom IL-6 concentration at the site of inflammation is higher than in the plasma, full blockade of plasma IL-6 activity, shown by complete CRP inhibition, is the minimum requirement to achieve clinical efficacy.

CRP inhibition with tocilizumab (TCZ) in pts with COVID-19. We identified 35 published studies evaluating the efficacy or potential role of anti-IL-6 therapy in pts with severe COVID-19. Surprisingly, only one (Luo et al. J Med Virol 2020;92:814) reported dynamics of CRP reduction for individual patients throughout treatment. We fitted a hypothetical curve of CRP reduction required to completely block IL-6, based on the half-life of CRP, and added data points of CRP serum levels from pts treated with anti-IL-6 receptor (IL-6R) therapy, TCZ, in this study. Complete reduction of CRP was not achieved in all patients: 3 pts who died had CRP levels ≥ 12.8 mg/l. Of 2 pts whose disease worsened, CRP levels were 93.5 mg/l and 6.3 mg/l. However, pts whose condition stabilized (n=9), or whose symptoms improved (n=1), had CRP levels close to the theoretical curve that is likely required to fully block IL-6 (CRP levels ≤ 5.0 mg/l). Half of these pts had been given repeated doses of TCZ.

Siltuximab (SIL) treatment (NCT01024036 trial) for pts with iMCD. To assess the impact of baseline CRP levels on response to anti-IL-6 therapy, SIL, patients were divided into low and high CRP groups based on a baseline CRP level threshold of 40 mg/l (corresponding to ~ 40 pg/ml of IL-6; Fig 1). In patients with low baseline CRP levels (<40 mg/l; n=35), CRP levels were significantly reduced with SIL treatment on day 8 (n=26; P=0.0003) and day 15 (n=22; P=0.0043) post-dosing. In patients with high baseline CRP levels (>40 mg/l; n=17), CRP levels were significantly reduced on day 8 (n=17; P<0.0001) and day 15 (n=15; P<0.0001) post-dosing (Fig 1). A significant increase in CRP levels from day 8 to day 15 was observed in these patients (P=0.0120); this increase was not observed in patients with low baseline CRP levels (P=0.243; Fig 1). There was a negative correlation between maximum CRP and hemoglobin change (P<0.001).

Inhibition of IL-6 activity by anti-IL-6 (SIL 700 mg) and anti-IL-6R (TCZ 800 mg) as monotherapy, intensified, or combined therapy. To evaluate the effect of therapy on IL-6 activity, our algorithm modeled inhibition of IL-6-(IL-6R/soluble IL-6R)-gp130

transducer complexes. This serves as a proxy for IL-6 bioactivity and accounts for the buffering capacity of gp130, which can be overwhelmed in inflammatory situations with high IL-6 concentrations. Due to uncertainty over the concentration of mAbs in alveoli relative to plasma, we modeled the effects of SIL and TCZ at local concentrations of 100%, 10%, and 1% (Fig 2) of those in plasma. Our model demonstrated that anti-IL-6 was associated with stronger inhibition of CRP than anti-IL-6R. However, only the association of both anti-IL-6 and anti-IL-6R mAbs was associated with a total blockade of CRP, which is probably necessary when IL-6 levels are associated with high risk to the patient. Different administration schedules to intensify anti-IL-6 therapy were modeled, including the repeated or combined use of anti-IL-6 and anti-IL-6R mAbs. The results form a basis to optimize treatment strategies to avoid the cytokine storm in several diseases, including cancer, iMCD, and autoimmune disorders. The feasibility of the theoretically defined approaches needs to be evaluated, particularly the potential side-effect profile for a combined treatment approach.

In conclusion, in clinical practice, IL-6 inhibition should be individualized based on pathophysiology and regular CRP monitoring.

Disclosures Rossi: *E-SANA Inc:* Other: Co-founder of E-SANA Inc ; *EUSA Pharma:* Consultancy; *LEO Pharma:* Consultancy; *NPO Petrovax Pharm:* Consultancy. **Levon:** *E-SANA Inc:* Other: Co-founder of E-SANA Inc. **Kanhai:** *EUSA Pharma:* Current Employment. **Fajgenbaum:** *EUSA Pharma:* Research Funding; *N/A:* Other: Holds pending provisional patents for 'Methods of treating idiopathic multicentric Castleman disease with JAK1/2 inhibition' and 'Discovery and validation of a novel subgroup and therapeutic target in idiopathic multicentric Castleman disease'; *Pfizer:* Other: Study drug for clinical trial of sirolimus.

OffLabel Disclosure: Siltuximab is approved for the treatment of iMCD. Tocilizumab is approved for the treatment of Rheumatoid arthritis, Giant cell arteritis, Cytokine release syndrome, Systemic juvenile idiopathic arthritis and Polyarticular juvenile idiopathic arthritis. Combination therapy using Siltuximab and Tocilizumab has not yet been approved.

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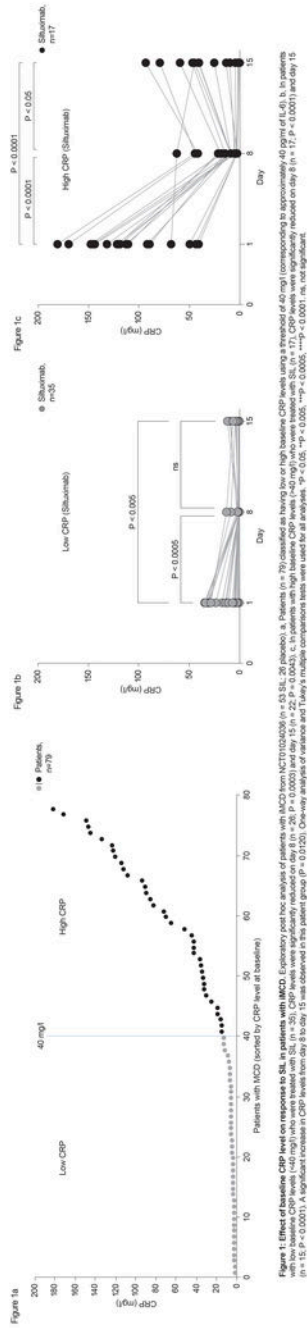


Figure 1. Effect of baseline CRP level on response to SL in patients with MCD. Respiratory post hoc analysis of patients with MCD from NCT02020209 (n = 53 SL, 26 placebo). a. Patients (n = 79) considered as having low or high baseline CRP levels using a threshold of 40 mg/l (corresponding to approximately 40 ng/ml of IL-6). b. In patients with low baseline CRP levels (<40 mg/l) who were treated with SL (n = 35), CRP levels were significantly reduced on day 8 (n = 20; P < 0.0005) and day 15 (n = 22; P < 0.0005). c. In patients with high baseline CRP levels (>40 mg/l) who were treated with SL (n = 17), CRP levels were significantly reduced on day 8 (n = 17; P < 0.0001) and day 15 (n = 15; P < 0.0001). A significant increase in CRP levels from day 8 to day 15 was observed in this patient group (P = 0.0125). One-way analysis of variance and Tukey's multiple comparisons tests were used for all analyses. *P < 0.05, **P < 0.005, ***P < 0.0005, ****P < 0.0001, ns, not significant.

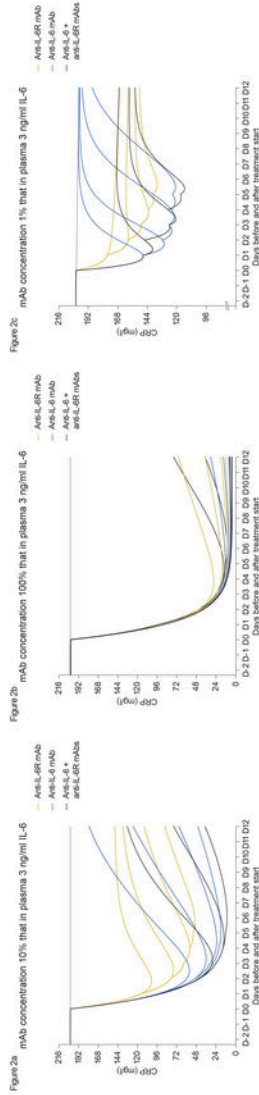


Figure 2. Mathematical modeling demonstrates the inhibition of IL-6 activity by an anti-IL-6 mAb, anti-IL-6R mAb, or their combination. Outputs of a mathematical model of subunit representation of human CCR5/IL-6, with a soluble agonist and soluble IL-6 (production of signal IL-6 in bronchoalveolar lavage fluid). Theoretical curves show the efficacy of SL, TCC, or a combination of the two mAbs in reducing CRP levels in the circulation (surrogate measure for IL-6 bioactivity). Inhibition of CRP is shown in response to repeated daily injections of anti-L-6R mAb (TCC, yellow), anti-L-6 mAb (SL, blue), or alternating daily injections of TCC and SL (black). Inhibition of CRP is shown in response to mAb concentrations at a, 10%, b, 100%, or c, 1% of the concentration in plasma. The gray line in panels shows IL-6 steady state with no treatment.

Figure 1