Clinical Infectious Diseases

CORRESPONDENCE

Response to 'Reduced Cell Surface Levels of C-C Chemokine Receptor 5 and Immunosuppression in Long Coronavirus Disease 2019 Syndrome'

To the Editor—Gaylis et al offer "an unexpected mechanism of abnormal immune downmodulation in some persons that is normalized by leronlimab" [1]. The disclosure of a public statement [2] and a Warning Letter [3] on leronlimab (PubChem SID 384585377) by the Food and Drug Administration (FDA) is appropriate. Gaylis et al offer no biostatistical methods but cite the clinical trial record. Using the Supplementary Data provided by Gaylis et al [1] with nonparametric Wilcoxon signed ranked test for change (Weeks 8–0), the 2-sided *P*-values for Figure 1*A* are .003 (leronlimab) and .0139 (placebo) and for Figure 1*B* are .0002 (leronlimab, Improving), .7344 (leronlimab, not improving), .0640 (placebo, not improving), and .1272 (placebo, not improving). Paired *t*-test results were not meaningfully different. Reporting nonsignificance (NS) for the latter 2 *P*-values with the given sample sizes is not advised, but the NS for placebo (Figure 1*A*) is significant and affects the conclusion. They do not define "responder" or state if the definition was made a priori. Some of the symptoms may not be independent (eg, cough/sore throat, headache/sleep disturbance) so using them all to generate a "responder" score should be explained. They fail to provide a mechanism of action or gene expression results to explain how a monoclonal antibody to CCR5, a G-protein-coupled receptor (GPCR), might increase the proportion of CD45+/CCR5+ T cells relative to total cell counts or increase expression of CCR5 in T cells. The authors should report the time between positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test and enrollment, duration of COVID-19 infection, re-exposure to SARS-CoV-2, especially to variants different from the original infecting viruses, other factors that affect immune responses, distribution of severity of COVID-19 among the treatment groups, the results by age and sex, the receptor occupancy, and the potential effects of the half-life of leronlimab. Galanti and Shaman [4] report multiple (re-)infections per year in the same subjects with other coronaviruses. Lee et al [5] reported that "granulocyte macrophage colony-stimulating factor caused a marked decrease of CXCR4 (from ~5000 ABS to <500) while up-regulating CCR5 expression (from ~5000 to ~20 000 ABS)." Jacobson et al [6] reported 'mean terminal half-lives (PRO 140 Serum Concentration) were 3.4 and 3.7 days, but Yang et al [7] suggested an "estimated half-life of about 10 days." With T-cell proliferation and the potential increase in CCR5 expression, the half-life and receptor occupancy need to be appropriately addressed in different patient populations. Roche and Futura state that "plasma membrane of eukaryotic cells is constantly being internalized" [8]; how long a 146.7 kDa [9] antibody bound to the 62 kDa [10] transmembrane CCR5 (NP_001381712.1) remains at the surface or, when it is internalized, whether it is trafficked back to surface or to the lysosomes is of interest. T-cell exhaustion [11] could help explain the results; with small sample sizes, imbalances can occur so duration, severity, and time from PCR test for each patient is important. Finally, genotypes of CCR5, which may affect binding of leronlimab, and of the ligands of CCR5, such as CCL3L1 with copy number variants [12], and any antidrug antibodies (ADA) against leronlimab would help elucidate this finding.

Note

Potential conflicts of interest. Stock or stock options: K. R. V. owns 10 shares of CytoDyn (CYDY). Other financial or nonfinancial interests: K. R. V. signed agreement that expires 2 July 2022 with a university to explore 2 patents covering CCR5 inhibition for indications not being pursued by CYDY (the patents expire in December 2024 and do not include a molecule). The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed

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References

1. Gaylis NB, Ritter A, Kelly SA, et al. Reduced cell surface levels of C-C chemokine receptor 5 and immunosuppression in long coronavirus disease 2019 syndrome [published online ahead of print, 2022 Apr 22]. Clin Infect Dis **2022**: ciac226.
2. Anonymous. Statement on Leronlimab. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/statement-leronlimab. 17 May 2021. Accessed 24 April 2022.
3. Haffer AST. WARNING LETTER CytoDyn, Inc. MARCS-CMS 626957—FEBRUARY 11, 2022. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cytodyn-inc-626957-02112022.02/22/2022. Accessed 24 April 2022.
4. Galanti M, Shaman J. Direct observation of repeated infections with endemic coronaviruses. J Infect Dis **2021**; 223:409–15.
5. Lee B, Sharron M, Montaner LJ, Weissman D, Doms RW. Quantification of CD4, CCR5, and CXCR4 levels on lymphocyte subsets, dendritic cells, and differentially conditioned monocyte-derived macrophages. Proc Natl Acad Sci USA **1999**; 96:5215–20.
6. Jacobson JM, Thompson MA, Lalezari JP, et al. Anti-HIV-1 activity of weekly or biweekly treatment with subcutaneous PRO 140, a CCR5 monoclonal antibody. J Infect Dis **2010**; 201:1481–7.
7. Yang B, Fulcher JA, Ahn J, et al. Clinical characteristics and outcomes of coronavirus disease 2019 patients who received compassionate-use leronlimab. Clin Infect Dis **2021**; 73: e4082–9.
8. Roche PA, Furuta K. The ins and outs of MHC class II-mediated antigen processing and presentation. Nat Rev Immunol **2015**; 15:203–16.
9. Anonymous. DRUG: Leronlimab. Available at: https://www.genome.jp/dbget-bin/www_bget?dr:D11399. Access April 24, 2022.
10. Suzuki S, Miyagi T, Chuang LF, Yau PM, Doi RH, Chuang RY. Chemokine receptor

CCR5: polymorphism at protein level. Biochem Biophys Res Commun **2002**; 296: 477–83.
11. Kahan SM, Wherry EJ, Zajac AJ. T cell exhaustion during persistent viral infections. Virology **2015**; 479-480:180–93.
12. Olsson LM, Holmdahl R. Copy number variation in autoimmunity–importance hidden in complexity? Eur J Immunol **2012**; 42:1969–76.

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