## Answer to "Confounding effect of cyclosporine dosing when comparing horse and rabbit antithymocyte globulin in patients with severe aplastic anemia"

We thank Dr. Bleyzac *et al*.[1] for their interest in our work and comments.[2] In their letter, the authors discuss a possible association between cyclosporine (CsA) dosing and hematologic response in aplastic anemia (AA). Their preliminary clinical data suggest that CsA blood levels between 87 and 120 ng/mL might increase responses due to a positive effect on regulatory T-cell numbers. They question whether CsA dosing could be a factor in our randomized study of horse and rabbit antithymocyte globulin (ATG) in severe AA.

Bleyzac *et al*. warn of "abusive" effects of conclusions concerning mechanism of action of ATGs based on our data,[1] but this was not our interpretation of our results either in the current work[2] or previously.[3] In both articles, we explicitly stated that differences in measurements of cytokines and lymphocyte phenotyping indicated differences in the *in vivo* activities of putatively similar biological therapeutics. Associations cannot be claimed as causative, nor can changes, for example in cell populations, be assumed to entail functional effects in humans.

For CsA levels, target concentrations were specified in the protocol and monitored at weekly intervals in both arms of our comparative trial, and they were generally similar in both the rabbit and horse ATG groups. We would doubt that CsA dosing or blood levels account for either our clinical or laboratory results.

The mechanism of immunosuppressive therapy in AA is still not understood in depth. The hypothesis proposed by the authors of the letter is of interest and deserves exploration. Together with our collaborators, we are currently working to refine phenotyping of regulatory T cells in AA.[4]

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### References

1. Bleyzac N, Philippe M, Bertrand A, Bertrand Y. Confounding effect of cyclosporine dosing when comparing horse and rabbit antithymocyte globulin (ATG) in patients with severe aplastic anemia. Haematologica. 2015;100(5):;e211-212.
2. Feng X, Scheinberg P, Biancotto A, et al. In vivo effects of horse and rabbit antithymocyte globulin in patients with severe aplastic anemia. Haematologica. 2014;99(9):1433-1440.
3. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011;365(5):430-438.
4. Kordasti S, Seidl T, Ellis RJ, et al. High Resolution Mass Cytometry (CyTOF) in Aplastic Anaemia (AA) Can Identify an Aberrant Treg Subset with Pro-Inflammatory Properties, Predicting Poor Response to Immunosuppressive Therapy. Blood. 2014;124(21):1600.