

ticle was limited to the physiological and immunologic events that occurred within 30 days after exposure; the omission cited by Gardner does not make the report incomplete.

Corry and Lewis suggest that the cytokine storm induced by TGN1412 is similar to that resulting in the toxic shock syndrome, on the basis of the activation of CD28 on T cells. Although T cells were the intended targets of TGN1412, it is still unclear whether T-cell activation induced the cytokine storm. The trigger may have been on another type of cell expressing CD28, as suggested by Puellmann et al., or may have involved ligation of Fc receptors. Hence the macrophage activation syndrome was also considered. Since the neutrophil count was preserved and, as noted by Garcia-Bournissen et al., there was neither hepatosplenomegaly nor lymphadenopathy, we thought that the macrophage activation syndrome as a separate entity should be ruled out. Our article was a clinical report of the unintended consequences of a phase 1 trial and subsequent emergency care. Laboratory investigations were limited to those that were of direct clinical benefit.

Anti-TNF therapy was considered. When transfer to our care took place 12 to 16 hours after TGN1412 infusion, we decided that the TNF peak was likely to have passed and that downstream events had already been triggered. As cytokine data became available, showing persistently high TNF levels, this decision was reviewed. In our minds, in the setting of severe lymphopenia and monocytopenia of unknown duration, treatment with high-dose corticosteroids and anti-interleukin-2 receptor antagonist antibody, and the increased risk of secondary infections in the patients, the risk of anti-TNF therapy still outweighed its potential benefit. We would be yet more cau-

tious with a cause associated with infection, such as the toxic shock syndrome.

We agree with Takita et al. Plasmapheresis was considered, but the known pharmacokinetics of a low IgG4 antibody level suggested that the drug would be tissue-bound. We also agree that there may be a role for continuous venovenous hemodiafiltration in blunting the cytokine storm associated with a severe systemic inflammatory response. Furthermore, high dialysate rates³ and high-cutoff filters⁴ have previously been suggested for use in treating sepsis. Our patients received continuous venovenous hemodiafiltration at an initial dialysate rate of 1 liter per hour, which was subsequently raised to 4 liters per hour, using standard membranes. In our opinion, aggressive multiorgan support and early institution of high-volume diafiltration and treatment with high-dose corticosteroids, combined with the physiological resilience of these six young, healthy research volunteers, were key to their survival.

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T-Cell Costimulation

TO THE EDITOR: In their Perspective article, Sharpe and Abbas (Sept. 7 issue)¹ discuss possible explanations for the adverse events associated with a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412, as reported by Suntharalingam et al.² Sharpe and Abbas suggest that a difference in affinity for CD28 between species may be important.¹ However, an alternative explanation relates to differences in Fc-receptor binding between

species, which is dependent on the isotype of the monoclonal antibody.³ It is for this reason that anti-CD3 monoclonal antibodies (signal 1) have been engineered to reduce Fc-receptor binding. This process results in less cross-linking of CD3 on the T-cell surface (through Fc-receptor binding) and consequently in little release of cytokines.⁴ TGN1412 is a human IgG4 monoclonal antibody. Previous studies in nonhuman primates have dem-

onstrated that this isotype is ineffective in engaging Fc receptors.⁵ Although TGN1412 was used at 1/500 of the dose that was used safely in nonhuman primates, increased avidity of the IgG4 Fc region for human Fc receptors may have caused sufficient cross-linking of CD28 to elicit a cytokine storm. Such a hypothesis could be tested experimentally.

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TO THE EDITOR: Sharpe and Abbas suggest that possible differences in the activation requirements of naive T cells and memory T cells could explain the lack of a biologic signal in animals. Another explanation, they say, is a possible difference in the affinity of the anti-CD28 monoclonal antibody for human and primate CD28 molecules. The accompanying article by Suntharalingam et al. does not discuss possible mechanisms of cytokine-storm induction but does note that similar reactions have been observed in previous trials of some antilymphocyte antibodies. A third possibility — distinct from the specificity of the antibody but more consistent with data from previous antibody trials,

which also showed cytokine release syndromes — is that cytokine release is induced by the binding of Fc to Fc receptors. Apart from the cytokine release syndromes, such binding would also induce the superactivation of T cells and would explain the immunopathology that is seen.¹

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THE AUTHORS REPLY: Wise et al. and Colaco note an additional possible mechanism for the cytokine release syndrome, related to Fc-receptor binding. Species differ greatly with respect to the number of Fc-receptor genes and specific cell-type expression patterns. We really do not understand the differences between nonhuman primates and humans with respect to the diversity of Fc receptors, and we lack information to make cross-species comparisons of the binding of human IgG subclasses to Fc receptors in nonhuman primates.¹ There is a need for better models to address these issues. It should be noted that differences in both the antibody subclass and the glycosylation status of the antibody influence the profile of Fc-receptor binding. In addition, human IgG4 has a low level of binding to Fc receptors but is not a non-binder. Clearly, it is important to consider the nature of the Fc portion of antibodies as they are developed for clinical use as therapeutic agents.²

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The State of Primary Care

TO THE EDITOR: In his Perspective article (Aug. 31 issue),¹ Bodenheimer accurately describes the assault on primary care medicine. Insurers deny payment and bureaucrats add onerous record keeping, while the needs of patients increase. We

persist only because of the rewards that are documented in the accompanying Perspective article by Woo.²

It seems unlikely that macrosystem improvement will occur in the near future. For small