The Review of DIABETIC STUDIES

COMMENTARY

Limitations in Immunotherapy with CD3 Antibodies: Comment on the Article by Drs. Chatenoud and Bach

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The article by Drs. Chatenoud and Bach [1] is in many aspects sophisticated as well as surging. It summarizes the latest findings on immunotherapy of type 1 diabetes (T1D) regarding the application of CD3 antibodies by scrutinizing four prevailing concepts that could mislead the further development of such therapies. Inasmuch these concepts, i.e. antigen-specific therapies, initiation of immunotherapy before diabetes onset, combining several agents and, finally, caution regarding the generalization of results obtained from NOD mice, still remain burning issues in diabetes research, the article contributes valuably to the path of finding the optimal intervention strategy. The authors present criticism to the four concepts and take a clear stand of the promise of antigen-nonspecific immunotherapy in the establishment of long-term remission. Insofar, the article inspires to a more intensive discussion to include aspects that could be able to enrich the discussion on these critical concepts.

Firstly, it is noticeable that the outcomes of several investigations do not confirm the role of anti-CD3 alone as a cure for T1D in humans [2-4]. If we act on this assumption, then either additional therapies and combinations will be needed or another holistic approach to cure the disease must be taken into consideration.

Another critical issue in anti-CD3 therapy is the dose of administration. The dose that is currently being used in clinical trials is probably close to the maximum that can be ethically given. This is because of the initial cytokine release syndrome and the transient EBV reactivation that occurs in many patients due to the systemically immunosuppressive properties of anti-CD3 [5-8]. In order to avoid high doses, more frequent administrations of anti-CD3 or administration during the prediabetic phase could be beneficial, although we do not know whether this strategy will be safe. In this regard, we may consider why the NOD animal model could be misleading. Although anti-CD3 did not completely protect from diabetes when given to prediabetic NOD mice, it did in other diabetes models, such as the streptozotocin-treated CD1 mice [9] and the rat insulin promoter-lymphocytic choriomeningitis virus (RIP-LCMV) model [10]. Therefore, maybe due to its multiple immune defects, the NOD mouse might not accurately reflect the immune status of the average prediabetic patient.

The statement that antigen-non-specific generalized immunosuppression is likely to cure T1D should be carefully weighed – although the benefit has been very clear in recent trials, we do not know at this point whether anti-CD3 alone will ever be able to prevent or cure T1D. Therefore, combination with other antigen-specific tolerogenic, systemically tolerogenic or islet regenerating treatments could be of benefit. Anti-CD3 does not act antigen-specifically as judged by the lack

 DOI 10.1900/RDS.2005.2.187

of results able to show that autoreactive T cells, which are associated with T1D, are indeed affected via treatment with the antibody. It is a systemic immune modulator, albeit with beneficial properties in autoimmune diseases. It induces a temporary generalized immunosuppression and is capable of enhancing the functional aspects of regulatory T cells (Tregs), which suggest that anti-CD3 may be a therapeutic agent suitable for interventions in T1D.

In general, it is our belief that we have to be cautious when translating results from animal models. It will ultimately help trial design and success rather than abolishing the need for animal models. However, there are some critical issues for a reliable translation to the clinic: (a) Anti-CD3 did not completely prevent the progression to disease in prediabetic NOD mice, but it did in other diabetic animal models [9, 10]. It is likely that the majority of human patients do not share all the immune defects existing in the NOD mouse and therefore anti-CD3 therapy might indeed be very effective in prediabetic patients. (b) Related with the previous point is the role of $CD25^+$ Tregs and their deficiency in humans with T1D. Whilst it is already clear that immunosuppressive $CD25^+$ Tregs are deficient in NOD mice [11], we are faced with conflicting reports on this issue in humans [12-14]. If these cells are not defective in humans, the human physiopathology should be different from that of NOD mice in many respects, and the study of other animal models could be helpful. (c) Finally, it is questionable how to translate the precise optimal dose from mice to humans. Drs. Chatenoud and Bach argue that there might be no value in lowering the anti-CD3 dose in 'mouse trials' to increase stringency [1]. Yet, the current dose of anti-CD3 administered to human patients is less effective (prevention of C-peptide decline temporarily, but no reversal of T1D) than the optimal dose in NOD mice, where virtually all diabetes cases have been found to be reverted permanently. Therefore, the administration of lower anti-CD3 doses to NOD mice might more realistically reflect the human situation. The question of optimal dose translation could be a critical factor here, as shown by trials of antigen administration within the Diabetes Prevention Trial 1 (DPT-1), where several forms of administration did not lead to promising results in humans [15, 16].

■ References

1. **Chatenoud L, Bach JF.** Questioning four preconceived ideas on immunotherapy of clinical type 1 diabetes: lessons from recent CD3 antibody trials. *Rev Diabetic Stud* 2005. 2(3):116-120.
2. **Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA.** Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 2002. 346(22):1692-1698.
3. **Keymeulen B, Vandemeulebroucke E, Ziegler AG, Mathieu C, Kaufman L, Hale G, Gorus F, Goldman M, Walter M, Candon S, et al.** Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med* 2005. 352(25):2598-608.
4. **Herold KC, Gitelman SE, Masharani U, Hagopian W, Bisikirska B, Donaldson D, Rother K, Diamond B, Harlan DM, Bluestone JA.** A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes* 2005. 54(6):1763-1769.
5. **Hirsch R, Gress RE, Pluznik DH, Eckhaus M, Bluestone JA.** Effects of in vivo administration of anti-CD3 monoclonal antibody on T cell function in mice. II. In vivo activation of T cells. *J Immunol* 1989. 142(3):737-743.
6. **Ferran C, Sheehan K, Dy M, Schreiber R, Merite S, Landais P, Noel LH, Grau G, Bluestone J, Bach JF.** Cytokine-related syndrome following injection of anti-CD3 monoclonal antibody: further evidence for transient in vivo T cell activation. *Eur J Immunol* 1990. 20(3):509-515.
7. **Alegre M, Vandenabeele P, Flamand V, Moser M, Leo O, Abramowicz D, Urbain J, Fiers W, Goldman M.** Hypothermia and hypoglycemia induced by anti-CD3 monoclonal antibody in mice: role of tumor necrosis factor. *Eur J Immunol* 1990. 20(3):707-710.
8. **Renard TH, Andrews WS, Foster ME.** Relationship between OKT3 administration, EBV seroconversion, and the lymphoproliferative syndrome in pediatric liver transplant recipients. *Transplant Proc* 1991. 23(1 Pt 2):1473-1476.
9. **Herold KC, Bluestone JA, Montag AG, Parihar A, Wiegner A, Gress RE, Hirsch R.** Prevention of autoimmune diabetes with nonactivating anti-CD3 monoclonal antibody. *Diabetes* 1992. 41(3):385-391.
10. **von Herrath MG, Coon B, Wolfe T, Chatenoud L.** Nonmitogenic CD3 antibody reverses virally induced (rat insulin promoter-lymphocytic choriomeningitis virus) autoimmune diabetes without impeding viral clearance. *J Immunol* 2002. 168(2):933-941.
11. **Wu AJ, Hua H, Munson SH, McDevitt HO.** Tumor necrosis factor-alpha regulation of CD4+CD25+ T cell levels in NOD mice. *Proc Natl Acad Sci U S A* 2002. 99(19):12287-12292.
12. **Kukreja A, Cost G, Marker J, Zhang C, Sun Z, Lin-Su K, Ten S, Sanz M, Exley M, Wilson B, et al.** Multiple immunoregulatory defects in type-1 diabetes. *J Clin Invest.* 2002. 109(1):131-140.
13. **Lindley S, Dayan CM, Bishop A, Roep BO, Peakman M, Tree TI.** Defective suppressor function in CD4(+)CD25(+) T-cells from patients with type 1 diabetes. *Diabetes.* 2005. 54(1):92-99.
14. **Putnam AL, Vendrame F, Dotta F, Gottlieb PA.** CD4+CD25high regulatory T cells in human autoimmune diabetes. *J Autoimmun* 2005. 24(1):55-62.
15. **DPT-1 Study Group.** The Diabetes Prevention Trial - Type 1 diabetes (DPT-1): implementation of screening and staging of

relatives. *Transplant Proc* 1995. 27(6):3377.
16. **Diabetes Prevention Trial - Type 1 Diabetes Study Group.** Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002. 346(22):1685-1691.