

Enhancement of the Affinity of Glucocorticoid Receptors as a Mechanism Underlying the Steroid-sparing Effect of Intravenous Immunoglobulin

To the Editor:

Intravenous immunoglobulin (IVIG) is commonly used for the treatment of a wide range of autoimmune diseases^{1,2,3}. The available data also suggest that IVIG has a steroid-sparing effect: either enhancing the steroid sensitivity or reducing the steroid dose^{4,5,6}. These reports indicate that IVIG can be considered as a therapeutic choice in steroid-resistant autoimmune and inflammatory diseases such as dermatomyositis, asthma, and polymyositis. We aimed to identify the underlying molecular mechanisms by which IVIG therapy can restore steroid sensitivity and can as a “steroid-sparing” agent.

We addressed the steroid-sparing effect of IVIG by analyzing the affinity of glucocorticoid receptor (GCR) using lymphoblastoid cell line CEM-C1. CEM-C1 is resistant to steroids despite its expression of functional GCR⁷ and hence represents an apposite model to study the steroid-sparing effect of IVIG.

Octagam® (Octapharma, Lingolsheim, France) was used as a source of IVIG in all the experiments. GCR-binding affinity was determined by [³H]-dexamethasone ([³H]-Dex) radioligand binding assays and Scatchard analysis⁸. The cells were incubated with increasing concentrations of [³H]-dexamethasone (Amersham Corp., Arlington Heights, IL, USA; range 0.1–50 nM) in the presence or absence of 500-fold excess of nonlabeled dexamethasone (Sigma Chemical Co., St. Louis, MO, USA) for 60 min. After incubation, the cells were rinsed, lysed, and counted in a β -spectrometer.

Pretreatment of CEM-C1 cells with IVIG followed by dexamethasone (10 μ M) led to an increase in apoptosis as compared to dexamethasone alone. We thus assessed whether this increase in sensitivity of CEM-C1 to dexamethasone was due to the changes in GCR-binding affinity during IVIG treatment. The baseline GCR dissociation constant (K_d) of CEM-C1 was at 7.36 nM level. Interestingly, after 2 h of IVIG treatment of cells, the mean K_d had significantly fallen to 3.12 nM (Figure 1), suggesting an enhancement of affinity for GCR by IVIG.

Longterm steroid use is associated with many debilitating adverse effects and hence several alternative steroid-sparing agents including cyclosporine and mepolizumab have been used^{9,10}. Many of these alternative treatments, such as cyclosporine, also have potentially harmful adverse effects. IVIG therapy has been reported to have steroid-sparing effects with relatively few adverse effects. The mechanisms involved in steroid-sparing effects of IVIG are not fully understood but may involve immunomodulation. Using a steroid-resistant CEM-C1 cell model, our results suggest that one of the steroid-sparing effects of IVIG is mediated through the improved GCR-binding affinity.

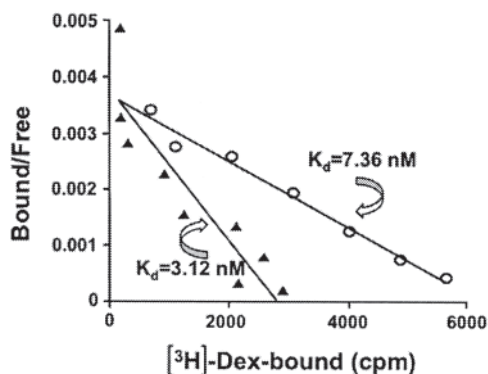


Figure 1. Scatchard analysis of [³H]-dexamethasone radioligand binding data of CEM-1 cells. Black triangles represent cells treated with 0.24 mM IVIG for 2 h.

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REFERENCES

1. Tha-In T, Bayry J, Metselaar HJ, Kaveri SV, Kwekkeboom J. Modulation of the cellular immune system by intravenous immunoglobulin. *Trends Immunol* 2008;29:608-15.
2. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol* 2010;6:129-37.
3. Stringer E, Bohnsack J, Bowyer SL, Griffin TA, Huber AM, Lang B, et al. Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey. *J Rheumatol* 2010;37:1953-61.
4. Spahn JD, Leung DY, Chan MT, Szeffler SJ, Gelfand EW. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 1999;103:421-6.
5. Zandman-Goddard G, Krauthammer A, Shoenfeld Y. The steroid-sparing effect of intravenous immunoglobulin in patients with autoimmune diseases. *Expert Rev Clin Immunol* 2007;3:773-80.
6. Marie I, Menard JF, Hatron PY, Hachulla E, Mouthon L, Tiev K, et al. Intravenous immunoglobulins for steroid-refractory esophageal involvement related to polymyositis and dermatomyositis: a series of 73 patients. *Arthritis Care Res* 2010;62:1748-55.
7. Hala M, Hartmann BL, Bock G, Geley S, Kofler R. Glucocorticoid-receptor-gene defects and resistance to glucocorticoid-induced apoptosis in human leukemic cell lines. *Int J Cancer* 1996;68:663-8.
8. Kam JC, Szeffler SJ, Surs W, Sher ER, Leung DY. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. *J Immunol* 1993;151:3460-6.
9. Johns KR, Littlejohn GO. The safety and efficacy of cyclosporine (Neoral) in rheumatoid arthritis. *J Rheumatol* 1999;26:2110-3.
10. Roufosse F, de Lavareille A, Schandene L, Cogan E, Georgelas A, Wagner L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol* 2010;126:828-35 e3.

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