**Immunoglobulin Therapy: Merely Immunoglobulin Replacement or Immunomodulator in Patients with Hypogammaglobulinemia?**

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**Background:** Immunoglobulin (Ig) replacement therapy is the mainstay of treatment for patients with primary and secondary hypogammaglobulinemia to prevent infections. High dose intravenous IgG is also used in many autoimmune and inflammatory diseases such as chronic inflammatory demyelinating polyneuropathy. Its function as anti-inflammatory agent has been reviewed (NEJM. 2012; 367(21): 2015-25) and a candidate receptor mediated mechanism of action identified (Nature 2011 Jun 19; 475(7354):110-3). However, it is not known whether IgG at a replacement dose have any T-cell modulatory effects, or is simply replacing IgG in patients with low levels.

**Objective:** To examine the effect of Ig replacement therapy on T-cell number, immunophenotype subset and functional markers in patients with hypogammaglobulinemia.

**Methods:** A prospective observational study is being conducted at the Ottawa Hospital Research Institute from October 2013 – December 2014. Forty patients with primary and secondary hypogammaglobulinemia will be recruited from the Ottawa Hospital Immune Deficiency Clinic. T-cell number, T-cell activation markers and serum cytokine levels will be studied before and one to two months after initiation of Ig replacement therapy using flow cytometry and Enzyme Linked Immuno Sorbant Assay. Ten healthy individuals will serve as internal control.

**Results:** To date, we have studied 3 patients with hypogammaglobulinemia. Their IgG levels were 6.4, 6.53, and 0.4 g/L compared to IgG levels from 2 healthy controls of 9.4 and 10.6 g/L. T cell numbers were similar in patients with hypogammaglobulinemia and healthy controls. Following in vitro stimulation with anti-CD3/CD28 antibody, CD4 T-helper cells and CD8 cytotoxic T cells from patients expressed the activation markers CD69 and CD38 at similar levels compared to T cells from healthy controls. Two months post IgG therapy, peripheral blood was obtained from one patient whose IgG level increased to 10.8 g/L from 6.8 g/L. Twenty-four hours following in vitro stimulation, there was a significant increase in the proportion of CD4 and CD8 T cells expressing the activation maker CD25 (79.1% CD25+CD4 compared to 29.6% before IgG therapy, and 72.8% CD25+CD8 compared to 49.3% before IgG therapy).

**Conclusion:** This is an ongoing research project. The results shown here are only preliminary, thus, it is premature to make any conclusion. However, it is possible that IgG replacement therapy is not merely replacing IgG in hypogammaglobulinemic patients and may in fact modify T-cell function.