Session 4: Autoimmunity

Wednesday 25 April 2001, Moderator: Professor Y. Schoenfeld

[11.00–11.40]

IVIG – What is its role in rheumatology?

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High dose γ-globulins were first employed in treating patients with immunodeficiencies. Following the observation of an increased number of platelets in a child with Wiscott-Aldrich syndrome treated with i.v. γ-globulin, the compound was used successfully in patients with autoimmune thrombocytopenia [idiopathic thrombocytopenic purpura (ITP)]. The positive results in ITP in children and adults prompted the introduction of this therapy in diverse autoimmune states including systemic lupus erythematosus (SLE), dermatopolymyositis, Guillain-Barre' syndrome, multiple sclerosis, rheumatoid arthritis and others. Recently we showed the efficacy of human IVIG as a treatment for the murine experimental model of anti-phospholipid syndrome (APS) and SLE [1,2]: IVIG prevented fetal loss in APS and abrogated the clinical manifestations of SLE. The efficacy of IVIG in 20 patients with SLE was detailed recently [3]. IVIG was found to affect autoimmune conditions through multifactorial mechanisms. These are divided into humoral mechanisms which include Fc blockade by the IVIG effects on autoantibody binding and production, via the idiotypic anti-idiotypic network, prevention of immune complex formation, and neutralization of microbial toxins. IVIG also exerts its effects via cellular mechanisms entailing immune modulation of T and B cell number and function, as well as inhibition of anti-inflammatory cytokine production. Recently we have shown the efficacy of IVIG to prevent tumor metastases [4]. We will describe the additional potential of IVIG in systemic sclerosis and vasculitides (e.g. WG,C-S syndrome and livedo vasculitis which is the human serum Ig fraction that is mainly composed of IgG prepared from plasma pools of over 15,000 healthy blood donors and is suitable for i.v. use).

References: [1] R. Bakimer, B. Guilburd, N. Zurgil, and Y. Shoenfeld, *Clin. Immunol. Immunopathol.* (1993), 69–97. [2] I. Krause, M. Blank, J. Kopolovic, A. Afek, I. Goldberg, Y. Tomer, and Y. Shoenfeld, *J. Rheumatol.* **226** (1995), 1068. [3] Y. Levy, Y. Sherer, A. Ahmed, P. Langevitz, J. George, F. Fabbrizzi, J. Terryberry, M. Meissner, M. Lorber, J.B. Peter, and Y. Shoenfeld, *Lupus* **8** (1999), 705–712. [4] Y. Shoenfeld, P. Fishman, *Int. Immunol.* **11** (1999), 1247–1251.

Disclose: This study was supported by Omrix Pharmaceuticals, Rehovot, Israel, and ARP Biomed, Israel.

[11.40–12.00]

Vaccination and autoimmunity – 'Vaccinosis': A dangerous liaison?

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The question of a connection between vaccination and autoimmune illness (or phenomena) is surrounded by controversy. A heated debate is going on regarding the causality between vaccines, such as measles and anti-hepatits B virus (HBV), and multiple sclerosis (MS). Brain antibodies as well as clinical symptoms have been found in patients vaccinated against those diseases. Other autoimmune illnesses have been associated with vaccinations. Tetanus toxoid, influenza vaccines, polio vaccine, and others, have been related to phenomena ranging from autoantibodies production to full-blown illness (such as rheumatoid arthritis (RA)). Conflicting data exists regarding also the connection between autism and vaccination with measles vaccine. So far only one controlled study of an experimental animal model has been published, in which the possible causal relation between vaccines and autoimmune findings has been examined: in healthy puppies immunized with a variety of commonly given vaccines, a variety of autoantibodies have been documented but no frank autoimmune illness was recorded. The findings could also represent a polyclonal activation (adjuvant reaction). The mechanism (or mechanisms) of

Human Antibodies 10 (2001) 23–24
ISSN 1093-2607 / $8.00

autoimmune reactions following immunization has not yet been elucidated. One of the possibilities is molecular mimicry; when a structural similarity exists between some viral antigen (or other component of the vaccine) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Other possible mechanisms are discussed. Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunization (e.g. Guillain Barre syndrome). We will present 4 cases of autoimmune phenomena following BCG vaccination. The issue of the risk of vaccination remains a philosophical one, since to date the advantages of this policy have not been refuted, while the risk for autoimmune disease has not been irrevocably proved. We discuss the pros and cons of this issue (although the temporal relationship (i.e. always 2–3 months following immunization) is impressive).

References: [1] Y. Shoenfeld, A. Aron-Maor, *J Autoimmunity* **14** (2000), 1–10. [2] A. Aharon-Maor, Y. Shoenfeld, *IMAJ* **2** (2000), 225–227. [3] Y. Shoenfeld, A. Aharon-Maor, Y. Sherer, *Clin. Exp. Rheumatol.* **18** (2000), 1–4. [4] Y. Shoenfeld, http/www.rheuma21st.com/archives/apls_shoenfeld_vaccination_revisited_html (11.9.2000), 1–6.

[12.00–12.30]

Naturally occurring cytotoxic human monoclonal antibodies

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Abstract not received.

[12.30–12.50]

B cell superantigen-like interaction of a subset of IVIG with phage-displayed human IgG and IgM originating from VH germ-line segments 3-23 and 3-30/3-30.5

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Intravenous immunoglobulin preparations (IVIG) represent the IgG repertoire of several thousand healthy donors. The beneficial use of IVIG in certain immunodeficiencies and autoimmune diseases has been proven, but it is not clear how IVIG functions at the molecular level. We sequenced 104 IgG and IgM clones specifically reacting with IVIG molecules derived by phage display and IVIG-panning from patients with autoimmune thrombocytopenia (AITP), SLE, Kawasaki disease (KD), Stevens-Johnson-Syndrome, and a healthy individual. Sequencing revealed that the most frequently used VH germline gene segments of all IVIG-selected Fabs (70/104, 67%) were 3-23 and 3-30/3-30.5. In contrast, only 3 out of 33 (9%) unselected controls originated from those genes. Comparing two libraries from a patient with KD prepared before and after IVIG treatment, the reactivity with IVIG was higher for clones generated after the therapy. The combined results suggest a favoured interaction of a subset of IVIG – respectively normal immunoglobulin repertoires – with B cell receptors derived from 3-23 and 3-30/3-30.5 gene segments. Importantly, those are the most frequently rearranged VH germ-line genes among human B cells. As light chains, antigen-specificity and the high variation in CDR3 showed only little influence on the selection by IVIG, this type of interaction is characteristic for a B cell superantigen and may significantly shape the B cell repertoire. Further experiments revealed that despite possible homologies, at least some of the contact residues on Fabs for IVIG must be different from those for the model superantigens Staphylococcal protein A and HIV gp120. The IVIG-selected Fabs may now be used to clone antibodies representative of this IVIG-subset to study their regulatory influence on the B cell repertoire during normal development and disease.