Introduction

Mechanism of Action of Tumor Necrosis Factor Antagonists

Recent advances in our understanding of the underlying biochemistry and biological actions of tumor necrosis factor (TNF) have provided further insight into the nature and role of anti-TNF agents in clinical practice. These agents have changed the paradigm for treating several inflammatory diseases while raising new questions about how differences in their structure, function, and biological activity may explain clinically important safety and efficacy differences among these agents.

Charles A. Dinarello (scientific chair) and I (clinical chair) had the pleasure of heading a distinguished panel of Canadian rheumatologists and immunologists to review the evidence and consider the following fundamental questions:

1. Do monoclonal antibodies to TNF have different biological effects compared to soluble TNF receptors?
2. What knowledge has accumulated from the biology of TNF, particularly secreted versus membrane forms of TNF, that might help explain the differential effects of anti-TNF-α monoclonal antibodies of the IgG1 class and soluble TNF receptor molecules?
3. What knowledge has accumulated from the various diseases treated with TNF blockers that may help explain the differential effect of monoclonal anti-TNF-α antibodies and soluble TNF receptor molecules?
4. What knowledge has accumulated from the biology of granulomatous infections and lymphomas that may help explain the differential effects of monoclonal anti-TNF-α antibodies and soluble TNF receptor molecules?

The roundtable discussion provided suggestions on how to move our understanding of the biological differences of TNF antagonists forward. Several new research initiatives were recommended to further elucidate the mechanism of action of these agents:

1. Clinical role/relevance of human antichimeric antibodies and human anti-human antibodies
2. TNF antagonists/inhibitors and the risk of lymphoma
3. Effect of interferon gamma and biologically active TNF
4. Signaling with regard to apoptosis
5. Cell death phenomenon: a definitive answer regarding antibody-dependent cellular cytotoxicity for infliximab, etanercept, and all soluble TNF receptors, *in vitro* and *in vivo*
6. Use of annexin scan in other indications than Crohn's disease for evidence of apoptosis, i.e., to confirm that etanercept does not work in Crohn's, and to rule out kinetics
7. Studies of the dynamics of macrophage migration or monocyte migration in and out of joints
8. TNF antagonists and granulomatous infections in both peripheral blood and tissue.

Understanding the role of membrane-bound (transmembrane) TNF-α versus secreted TNF-α [1,2] emerged as an important, recurring theme in discussions of mechanisms of apoptosis as related to efficacy in the treatment of Crohn's disease, rheumatoid arthritis, and granulomatous diseases; and whether these same mechanisms affect susceptibility to infection by intracellular microorganisms and non-Hodgkin's lymphomas. A subtext to this discussion: whether there are differential effects of TNF blockers on transmembrane TNF-α expressed on T cells and macrophages. It was noted that a growing body of evidence[3-5] supports the concept of T cell apoptosis following infliximab therapy in Crohn's disease, whereas few studies have examined whether apoptosis occurs in patients with rheumatoid arthritis treated with either monoclonal anti-TNF-α antibodies or soluble TNF receptors. This question has particular importance for understanding differences in infections from intracellular microorganisms between infliximab and etanercept[6].

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EDWARD C. KEYSTONE, MD, FRCPC,
Professor of Medicine, University of Toronto,
Director, The Division of Advanced Therapeutics,
The Rebecca MacDonald Centre for Arthritis
and Autoimmune Disease,
Mount Sinai Hospital,
Josef and Wolf Lebovic Building,
60 Murray Street, 2nd Floor,
Toronto, ON M5T 3L9 Canada
E-mail: edkeystone@mtsinai.on.ca

CHARLES A. DINARELLO, MD,
Division of Infectious Disease,
University of Colorado Health Sciences Center,
Denver, Colorado, USA

ROUNDTABLE PARTICIPANTS:

Clinical Program Chair: Edward C. Keystone, MD, FRCPC, Professor of Medicine, University of Toronto, Toronto, Canada; Scientific Program Chair: Charles A. Dinarello, MD, Professor of Medicine, University of Colorado, Denver, CO, USA. Faculty: Stefan Ehlers, MD, Research Center Borstel, Division of Molecular Infection Biology, Borstel, Germany; Douglas R. Green, PhD, Adjunct Professor of Biology, La Jolla Institute for Allergy and Immunology, University of California, San Diego, CA, USA; Boulos Haraoui, MD, FRCPC, Clinical Associate Professor of Medicine, Université de Montréal, Montreal, Canada; Ivan Nestorov, PhD, Fellow, Amgen, Inc., Thousand Oaks, CA, USA; Paul P. Tak, PhD, MD, Professor of Medicine, Director, Division of Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam; Jan M.H. van den Brande, MD, Fellow, Gastroenterology, Laboratory for Experimental Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands. Canadian Advisors: André Beaulieu, MD, FRCPC, Division of Rheumatology, Centre Hospitalier de l'Université Laval, St-Foy; Jan P. Dutz, MD, FRCPC, Assistant Professor, Division of Dermatology, University of British Columbia, Vancouver; Hani El-Gabalawy, MD, FRCPC, Professor, University of Manitoba, Winnipeg; Frank R. Jirik, MD, FRCPC, Professor, Department of Biochemistry and Molecular Biology, University of Calgary, Calgary; Walter Maksymowych, MB, ChB, FACP, FRCPC, FRCP (UK), Professor of Medicine, University of Alberta, Edmonton; Janet E. Pope, MD, FRCPC, Associate Professor of Medicine, Epidemiology and Biostatistics, University of Western Ontario, London; Proton Rahman, MD, FRCPC, Assistant Professor of Medicine, Memorial University, St. John's; Robert K. Rottapel, MD, FRCPC, Associate Professor, Departments of Immunology, Medical Biophysics and Medicine, University of Toronto, Toronto; John T. Sibley, MD, FRCPC, Professor of Medicine, University of Saskatchewan, Saskatoon; Brian J. Underdown, PhD, MDS Capital Corp. and University Medical Discoveries, Inc., Toronto, Canada.

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