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TDAR as an early safety assessment for combination therapy

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Abstract

The rodent T-cell-dependent antibody response (TDAR) assay is used to assess the effect of candidate therapeutic agents on the immune system by measuring primary and secondary IgM and IgG antibody responses to exogenous antigen challenge. TDAR responses require intact function of multiple immune cells including antigen presenting cells and T and B lymphocytes, as well as a cytokine-dependent isotype class switch from IgM to IgG, resulting in production of an antigen-specific antibody response. Alterations in the amount of antibody produced therefore can reflect effects on any or all of the cell populations involved in TDAR. TDAR is commonly used in preclinical drug development especially where increased cause for concern exists (ICH guideline S8). Development of combination therapy that engages multiple targets impacting the immune system poses unique opportunity for increased efficacy but also unique risk for increased immunotoxicity. For this work, a mouse TDAR evaluating primary and secondary KLH antibody responses in a KLH-Specific IgM and IgG sandwich enzyme-linked immunosorbent assay (ELISA) was used to assess immunotoxicologic potential of multiple single and combination therapies. Combination therapy did not result in enhanced TDAR immunotoxicity compared to single therapy alone for the molecules evaluated. Tier 1 immunotoxicology assessments similar to those in standard toxicity studies were added to the TDAR assessment. Together, our data support the use of the TDAR assay for early safety assessment of potential combination therapies.

Biography

Amy L. Volk is Senior Associate Scientist in Biologics Toxicology, Biotechnology Center of Excellence at Janssen Research & Development, LLC. She works within the Immunotoxicology/Experimental Pathology group, providing expertise and support for biologics specific issues, including nonclinical safety/toxicology assessments for biopharmaceutical and cell-based therapeutic products. Amy joined Johnson & Johnson (Centocor) in 1997 and has contributed to a number of development programs, specifically in the immunology and oncology therapeutic areas. Amy is a graduate of a dual-degree program at Harcum College and the University of Pennsylvania School of Veterinary Medicine, as well Villanova University's BSN and LaSalle University's MPH programs.