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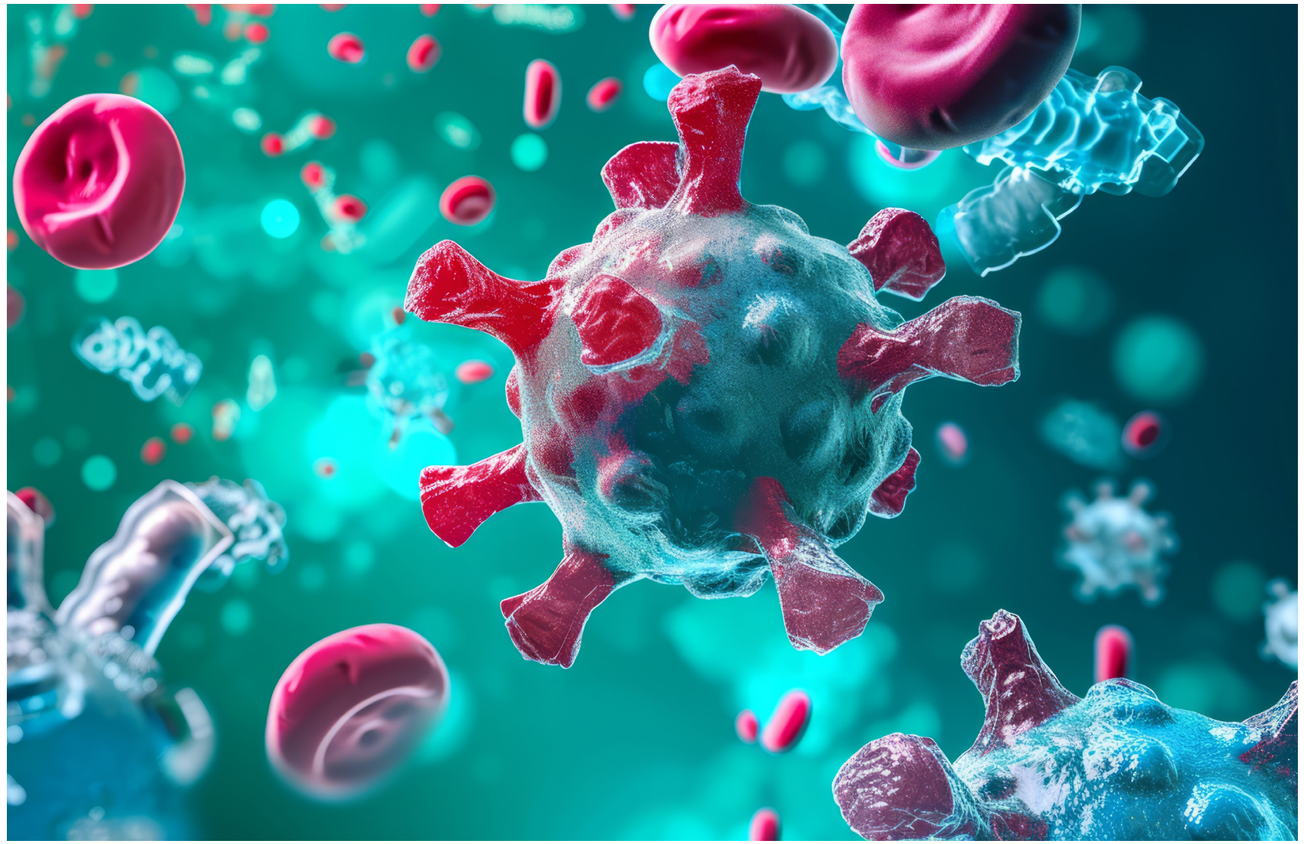

# Immunogenicity Concerns in Preclinical Safety Evaluation of Biologics in Sprague-Dawley Rats

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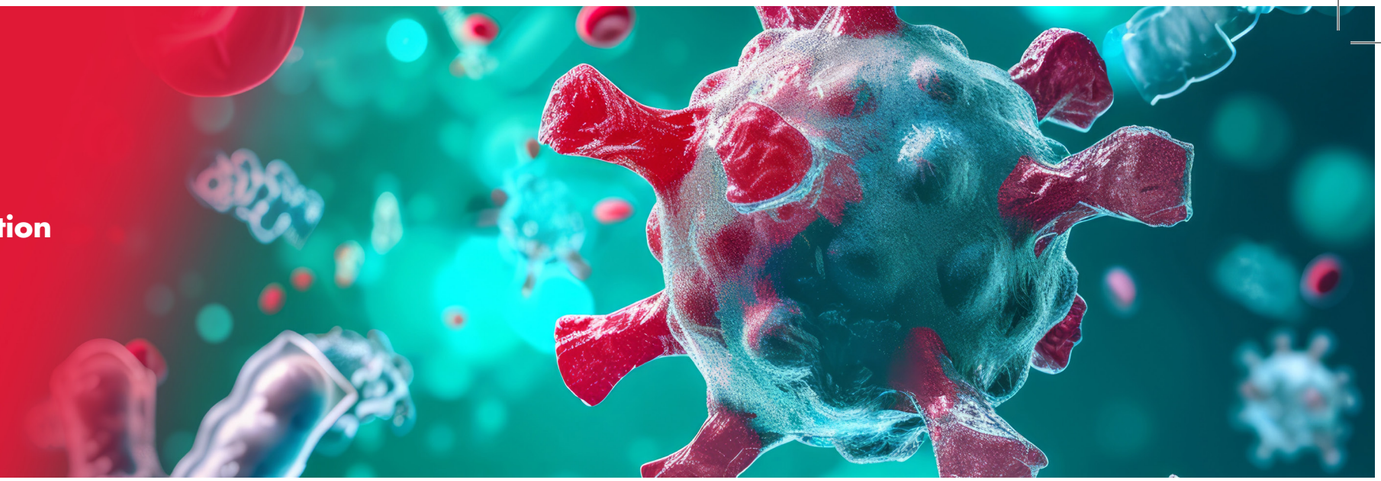

## INTRODUCTION

The development of biologics such as monoclonal antibodies (mAbs), bispecific antibodies, fusion proteins etc., have recently contributed significantly to the improvement of medical treatment of various diseases related to cardiovascular system, respiratory system, cancer, hematopoietic disease, autoimmune disease etc. Animal studies with the Sprague-Dawley (SD) rat is a common and valuable tool for safety evaluation of biologics. However, immunogenicity is still a concern and/or challenge when a safety evaluation study for biologics is conducted in rats which may compromise the predictive value for human adverse effects. However, rats do have good predictive value for human pharmacodynamics, and toxicological impacts. The purpose of this review was to assess the preclinical data of biologics toxicity studies to investigate immunogenicity of biological products.

## METHODS

To verify and support this recent assessment of immunogenicity in rats due to biologics exposure, we performed a retrospective evaluation of 18 toxicity rat studies conducted with biologics at the JOINN Laboratories site in Suzhou China during the last 5 years. The main endpoints analyzed included in-life animal information, biological treatments, clinical signs, body weight changes, duration of immunogenicity, and related-laboratory indexes such as clinical pathology, cytokines, and antidrug antibodies (ADAs), as well as medical interventions.

## RESULTS

The data analyses revealed that biologics safety studies were mostly performed at dose levels of 0.1 to 450 mg/kg in SD rats with animal ages ranging from 7 to 9 weeks. Immunogenicity was not dose-dependent and/or age-related in commonly used animal groups for safety evaluation. However, animal response to immunogenicity was dose-related and varied largely based upon the biological targets.

## RESULTS

Immunological response (anaphylactic reactions) mostly occurred about 2-3 weeks (>65%) after dose initiation and persisted throughout the dosing duration with certain biologics being adapted after repeated exposure. The data analyses revealed that biologics safety studies were mostly performed at dose levels of 0.1 to 450 mg/kg in SD rats with animal ages ranging from 7 to 9 weeks. Immunogenicity was not dose-dependent and/or age-related in commonly used animal groups for safety evaluation. However, animal response to immunogenicity was dose-related and varied largely based upon the biological targets. Immunological response (anaphylactic reactions) mostly occurred about 2-3 weeks (>65%) after dose initiation and persisted throughout the dosing duration with certain biologics being adapted after repeated exposure. The anaphylactic reactions were observed from immediately post-dose through days before next dose with incidences observed between 10% to 75% of animals, once immunogenicity was triggered. Commonly observed abnormal clinical symptoms included pale face and gingiva, decreased body weight, asthenia, hunched back, tachypnea, gasping, mouth breathing, and red nasal discharge, etc. Occasional animal death observed (up to 8.3%) due to acute anaphylactic reactions and/or body condition decline, which were likely induced by drug-ADAs-mediated hypersensitivity and/or cytokine release. When immunogenicity was triggered, biologics-related clinical pathology findings were commonly observed including decreased hemoglobin and hematocrit ranging from 3% to 26%, decreased lymphocyte counts ranging from about 8% to 26 % and increases in PT, APTT and FIB (ranged from 6% to 37%). Additionally, clinical chemistry changes of decreased albumin (ranged from 8.2% to 32%) and total protein (ranged from 8.3% to 18.6%), increased LDH, AST, ALT, ALP and/or CHO (ranged from 18.6% to 98%), were observed among the biologics-treated animals.

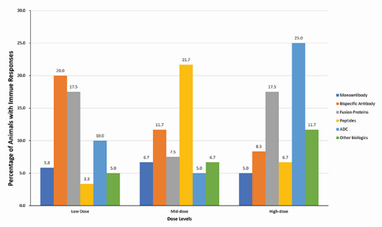


**Fig 1** Summary of Immune Response in Animals after Dosing for 2 to 4 Weeks

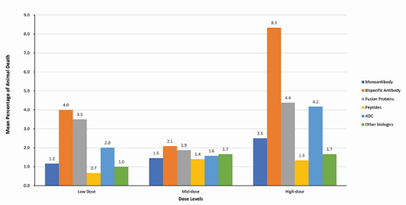


**Fig 2** Summary of Mortality in Animals after Dosing

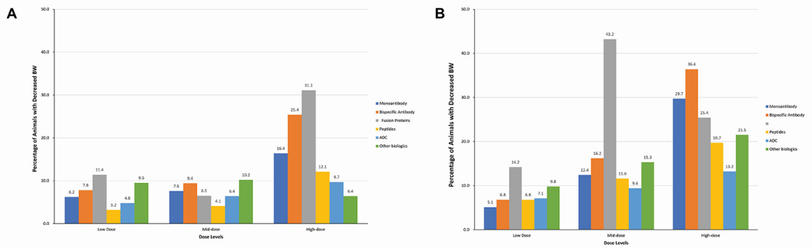


**Fig 3** A. Decreased Body Weight Levels in Animals after Dosing for 2 to 4 Weeks. B. Decreased Body Weight Levels in Animals Found Dead after Dosing.

## RESULTS

Cytokine detections as a sensitive indicator of immunogenicity were analyzed, although they are not solely attributed to anaphylactic reactions. Cytokine changes which correlated to immunogenicity included increased IL-6 level (ranged from 2% to 36%).

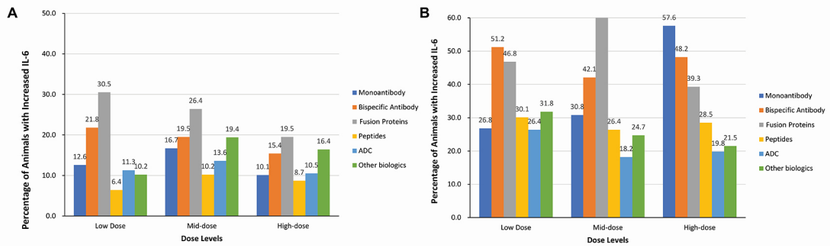


**Fig 4** A. Increase in IL-6 Levels in Animals after Dosing for 2 to 4 Weeks. B. Increase in IL-6 Levels in Animals Found Dead after Dosing.

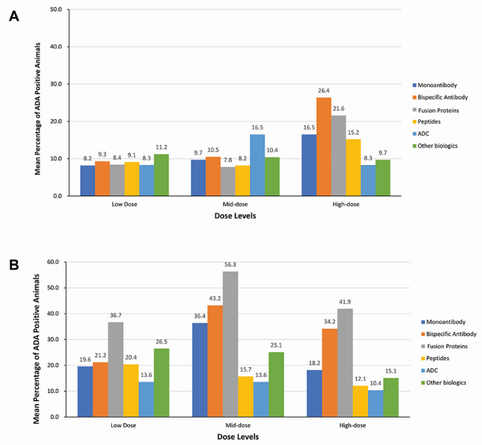


**Fig 5** A. Anti-drug Antibodies (ADA) Levels in Animals after Dosing for 2 to 4 Weeks. B. ADA Levels in Animals Found Dead after Dosing.

## CONCLUSION

The results of this review showed that although SD rats have good predictive value for human pharmacodynamics and toxicological impacts of biologics in safety evaluation, the animal responses of immunogenicity may impact toxicity assessment due to similarity in clinical signs and laboratory indexes of toxicity.