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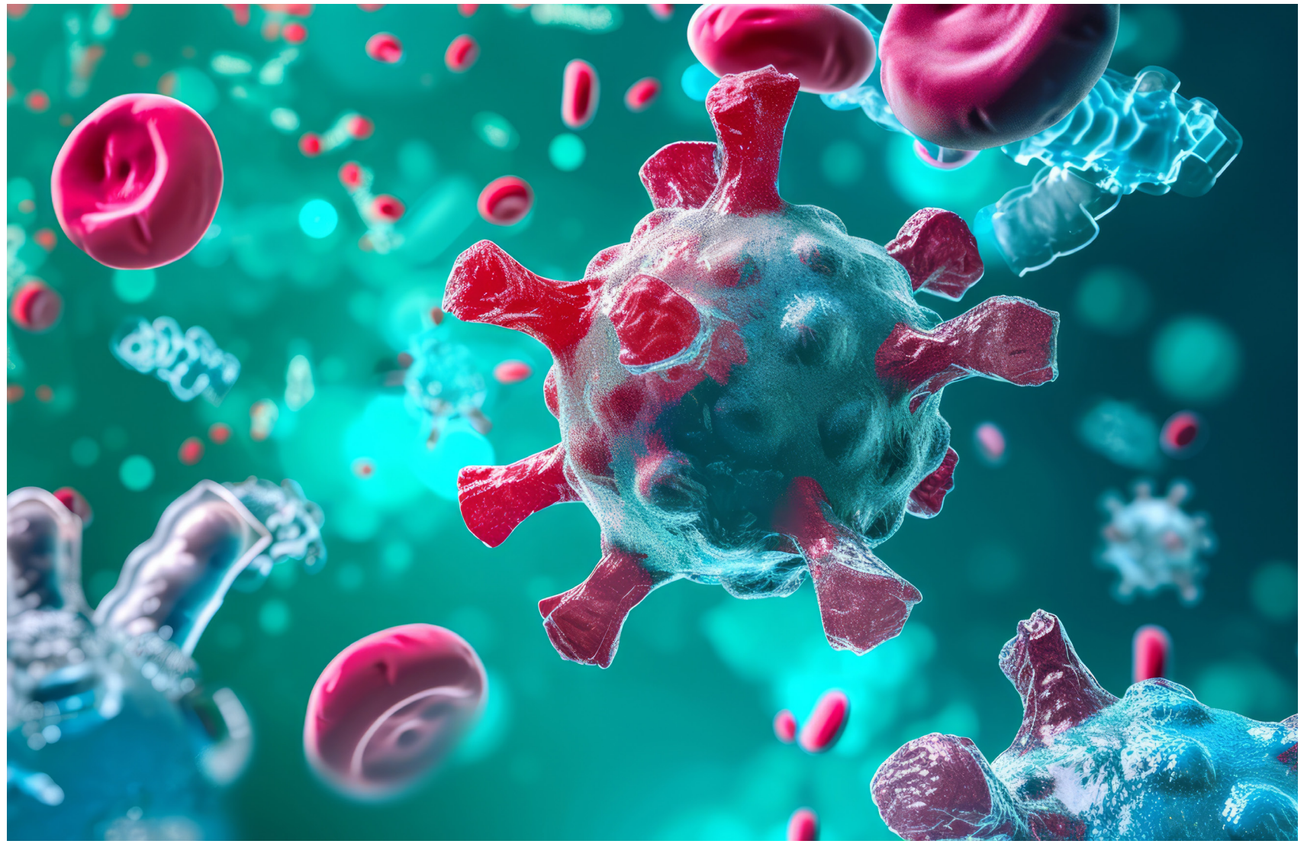

Immunogenicity Concerns in Preclinical Safety Evaluation of Biologics in Non-human Primates

Luke Zhang, Sucai Zhang, Yanlin Zhang, Yongbin Zhang
JOINN Laboratories (Suzhou) Co., Ltd

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JOINN Laboratories | www.joinnlabs.com
Contact: bd@biomere.com

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JOINN Laboratories (Suzhou) Co., Ltd
Contact: Yongbin Zhang, zhangyongbin@joinn-lab.com | www.joinnlabs.com

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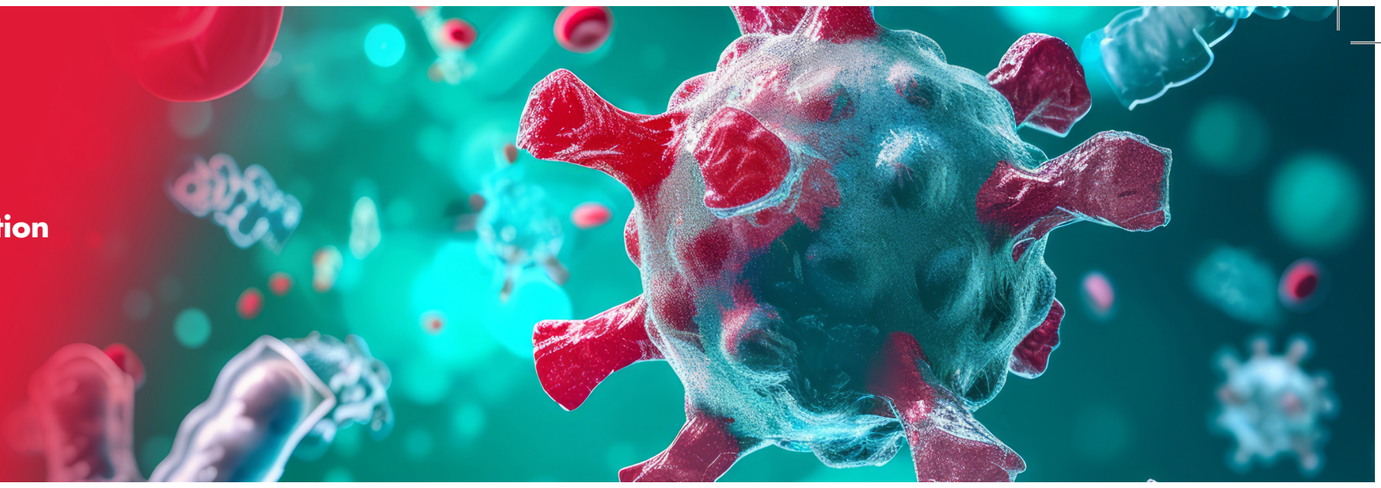

INTRODUCTION

Biological drugs such as monoclonal antibodies (mAbs), bispecific antibodies, and fusion proteins directed towards soluble biological targets make a great improvement in medical therapy of difficult to treat or rare diseases. Non-human Primates (NHPs) have been demonstrated to be a valuable animal species for preclinical safety evaluation of biologics, as they have good predictive value for pharmacodynamics, toxicological impacts, and physiological effects, However, immunogenicity is still a big concern for safety evaluation of biologics conducted in NHPs that can may compromise the predictive value for human adverse effects. This study aims to present specific parameters or methods for immunogenicity recognition and intervention regime in preclinical safety evaluation studies of biological products.

METHODS

To explore and assess immunogenicity of biologics in preclinical safety evaluation performed in NHPs, data from 245 preclinical toxicity studies conducted in the past 5 years to evaluate biologics safety were analyzed. A series of parameters including animal information, clinical signs, immunogenicity, and related-laboratory indexes such as clinical pathology, cytokines, circulating immune complex (CIC) and antidrug antibodies (ADAs), as well as medical interventions were analyzed.

RESULTS

The data analysis revealed that biologics safety studies were mostly performed at dose levels of 5 to 300 mg/kg in NHPs with animal ages ranging from 1.2 to 5 years. Immunogenicity was not dose-dependent and/or age-related in the commonly used animal groups for safety evaluation and was not associated with body weight. 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 weeks (>95%) after dose initiation and persisted throughout the dosing duration with certain biologics being adapted after repeated exposure. The anaphylactic reactions were mostly acute and transient abnormal reactions occurred within 30 minutes after the start of dosing with incidences observed between 20% to 100% of animals, once the immunogenic response was triggered. Commonly observed abnormal clinical symptoms included pale cheek and gingiva, asthenia, lethargy, prostration, tachypnea, gasping, mouth breathing, coughing, retching, red nasal discharge, red emesis and red spots on skin, etc. Some animals died rapidly (up to 19.2%) due to acute pulmonary failure or shock, which were induced by drug-ADAs-mediated hypersensitivity and/or cytokine storm. The animal deaths were considered to be biologics-induced hypersensitivity reactions, a phenomenon that does not translation to humans who are exposed to antibodies. When immunogenicity was triggered, biologics-related clinical pathology findings were commonly observed including mild changes in red blood cell (RBC)-related parameters with decreased RBC counts, hemoglobin, hematocrit ranging from 5% to 20% and increased Retic counts, decreased lymphocyte counts ranging from about 10% to 55 %. increases in PT, APTT and FIB (ranged from 7% to 28%). Additionally, clinical chemistry changes of decreased Albumin (ranged from 13% to 27%) and A/G (ranged from 13% to 27%), increased globulin (ranged from 10% to 69%), were observed among the biologics-treated animals.

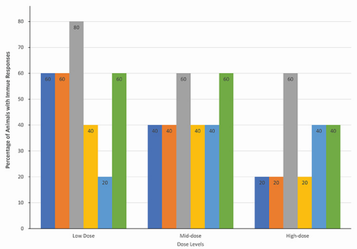

Fig 1 Summary of Immune Response in Animals after Dosing for 2 to 4 Weeks

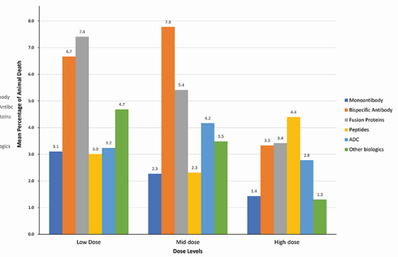

Fig 2 Summary of Mortality in Animals after Dosing

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, IL-10, and IL-12 p40 levels (ranged from 6% to 52%), as well as decreased complement protein (C3 and C4, ranged from 3% to 32%). Meanwhile, increased total immunoglobulin G, and CIC were detected.

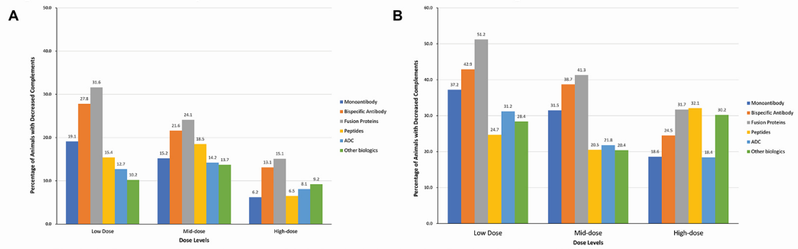

Fig 3 A. Decreased Complements (C3 & C4) in Animals after Dosing for 2 to 4 Weeks. B. Decreased Complements (C3 & C4) in Animals Found Dead after Dosing.

RESULTS

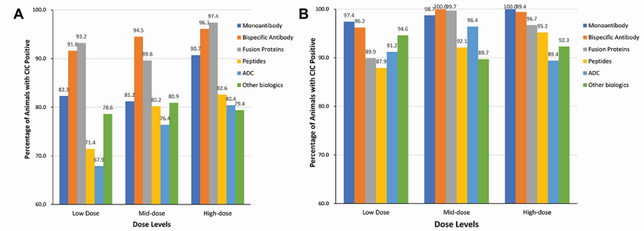

Fig 4 A. Increased Rates of CIC in in Animals after Dosing for 2 to 4 Weeks. B. Increased Rates of CIC in Animals Found Dead after Dosing.

Most animals had detectable positive ADAs (ranged from 70% to 100%), suggesting biologics were immunogenic in NHPs, however, the immunogenic reactions in this species are not predictive of similar human risk for humanized biologics like antibodies. Additionally, the results indicated that generation of ADAs might result in decreases in systemic exposure of biologics. Collectively, the above information provides reference for biologics safety evaluation in preclinical toxicity studies in NHPs. Additionally, the data analyses showed that anti-anaphylactic treatment on dosing day shortly after dose administration significantly reduced symptoms of immunological responses, indicating the anaphylactic reactions of animals were effectively inhibited or alleviated. However, the treatment might not be effective in some cases with severe hypersensitive reactions, especially during late stage (> 3weeks) of dose administration, which mostly required anti-anaphylactic pretreatment on the dosing days.

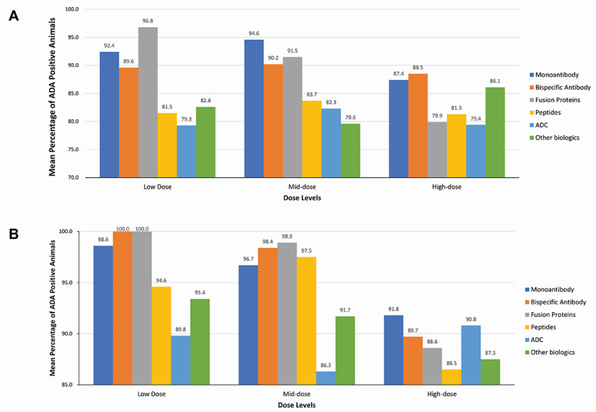

Fig 5 A. Anti-drug Antibodies (ADA) Levels in Animals after Dosing for 2 to 4 Weeks. B. ADA Levels in Animals Found Dead after Dosing.

CONCLUSION

The results showed that although non-human primates have good predictive value for human pharmacodynamics, toxicological impacts, and physiological effects of biologics, but no evidence indicate that NHPs have superior predictive value for human adverse immunological effects.