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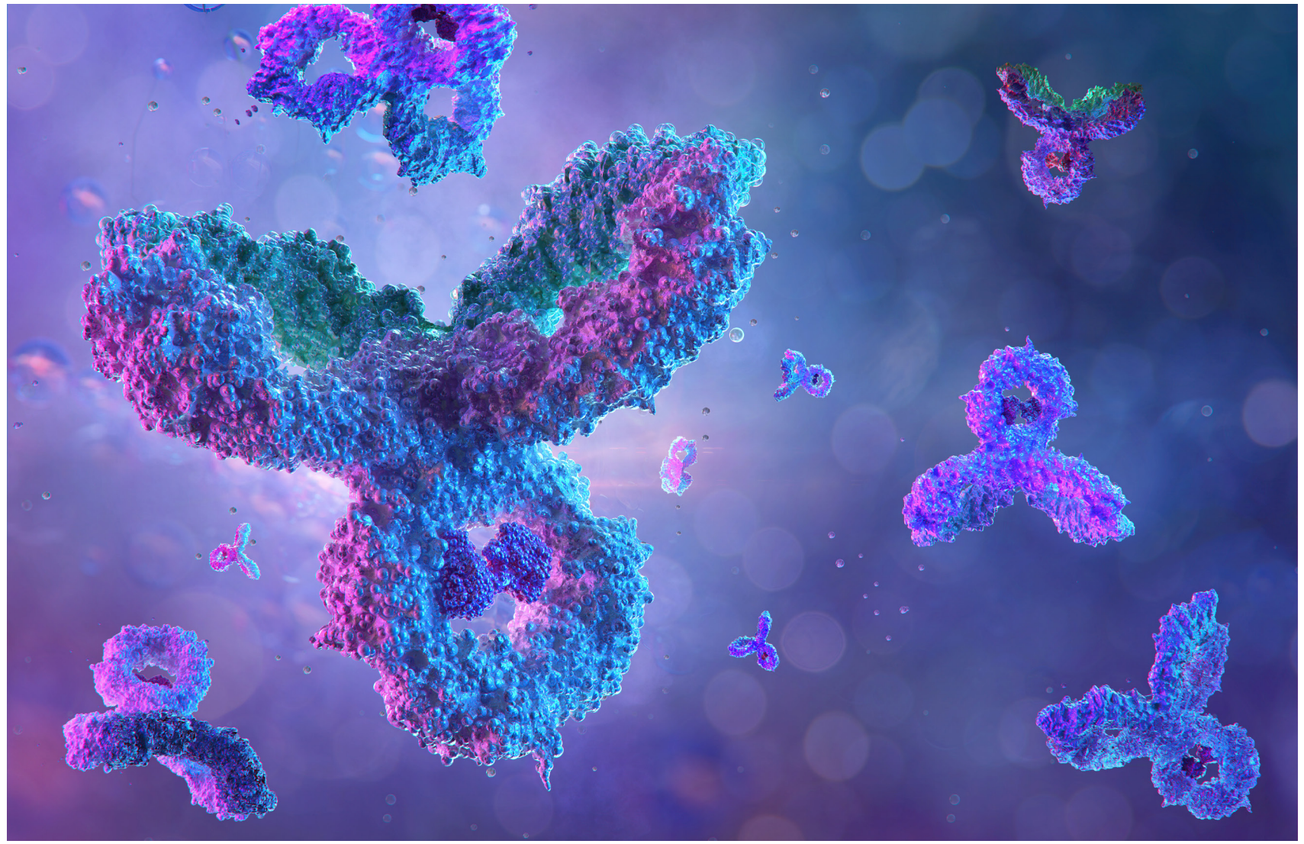

Immunogenicity Concerns in Preclinical Safety Evaluation of Biologics in Non-human Primates

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ABSTRACT

Biological drugs like monoclonal antibodies (mAbs), bispecific antibodies, and fusion proteins significantly improve treatments for difficult or rare diseases. Non-human primates (NHPs) are commonly used in preclinical safety evaluations due to their predictive relevance for pharmacodynamics, toxicology, and physiology. However, immunogenicity remains a critical concern, potentially compromising predictive accuracy for human adverse reactions. This study examines parameters and methods to identify and manage immunogenicity in preclinical safety studies of biologics.

Data from 245 NHP toxicity studies conducted over five years were analyzed, assessing animal demographics, clinical signs, immunogenicity, laboratory parameters (clinical pathology, cytokines, circulating immune complex (CIC), anti-drug antibodies (ADAs), and medical interventions.

The toxicity studies indicated that various biologics were tested at doses between 5 to 300 mg/kg in NHPs aged 1.2 to 5 years. Immunogenicity occurrence was independent of dose, age, or body weight, but responses varied by biological target and were dose-related. Anaphylactic reactions generally occurred within two weeks post-dose initiation, persisting or adapting over time. Clinical symptoms included pale cheeks, lethargy, respiratory distress, and rapid-onset death (up to 19.2%) due to ADA-mediated hypersensitivity or cytokine storms. Laboratory findings associated with immunogenicity included changes in RBC and lymphocyte counts, clotting parameters and hemoglobin, albumin, globulin, cytokine, immunoglobulin and complement protein levels.

Anti-anaphylactic treatments administered shortly after dosing significantly reduced immunological symptoms, although less effective for severe reactions after three weeks.

Our data suggests that NHPs effectively predict pharma-codynamics and toxicity but do not reliably predict human immunogenic responses to biologics.

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. 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 cheeks 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. 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. 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 (> 3 weeks) of dose administration, which mostly required anti-anaphylactic pretreatment on the dosing days.

CONCLUSION

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

RESULTS

Table 1 Summary of Study Information and Immunogenicity

Test Article Types	Number of Studies	Dose Levels (mg/kg)	Total Number of Animals: Used in Studies	Total Number of Animals: Immune Response Observed	Total Number of Animals: Hyper-sensitivity related Death	Anaphylactic Reaction Observed (Days)	Time Anaphylactic Reaction Occurred (Mins)	Age Range of Animals (Years)	Interventions Provided (%)
Monoantibody	62	3 to 280	2232	1172	70	13 to 28	2 to 68	2.4 to 5.1	24.2
Bispecific Antibody	43	1 to 450	1548	813	146	11 to 18	1 to 22	2.1 to 4.6	48.8
Fusion Proteins	28	3 to 300	1008	529	79	9 to 15	5 to 36	1.2 to 4.3	57.1
peptides	32	0.5 to 400	1152	605	48	17 to 32	5 to 53	1.4 to 5.2	21.9
ADC	12	5 to 450	432	227	20	15 to 27	4 to 36	2.7 to 4.1	16.7
Other biologics	68	0.3 to 250	2448	1285	154	10 to 37	2 to 41	1.4 to 3.8	17.6
Total	245	NA	8820	4631	518	NA	NA	NA	NA

Table 2 Main Clinical Signs in Animals with Immunogenicity (%)

Test Article Types	Number of Studies	Low-Dose: Tach /Gasp	Low-Dose: Asth /Leth	Low-Dose: Pale	Low-Dose: Rash /Eryt	Mid-Dose: Tach /Gasp	Mid-Dose: Asth /Leth	Mid-Dose: Pale	Mid-Dose: Rash /Eryt	High-Dose: Tach /Gasp	High-Dose: Asth /Leth	High-Dose: Pale	High-Dose: Rash /Eryt
Monoantibody	31	36.8	26.4	34.5	38.7	37.5	24.60	36.5	31.4	16.4	12.8	25.3	21.7
Bispecific Antibody	20	42.5	36.8	38.7	40.2	39.6	26.40	39.7	36.9	21.7	16.9	30.6	30.6
Fusion Proteins	13	39.4	41.2	39.1	31.9	40.2	35.80	42.6	46.7	19.5	15.4	28.7	35.7
Peptides	16	21.4	18.6	24.6	20.8	26.4	19.60	25.8	32.4	12.3	8.9	12.8	19.6
ADC	8	16.7	12.7	19.6	26.4	18.7	21.80	30.9	29.8	15.3	11.6	8.7	14.5
Other biologics	34	19.6	21.3	17.8	24.8	22.5	13.10	26.4	21.4	11.7	6.5	9.4	13.6

Note: Tach/Gasp = Tachypnea/Gasping; Asth/Leth = Asthenia/Lethargy; Rash/Eryt = Rash/Erythema

Table 3 Main Changes of Hematology Correlating with Dose Levels (% of Animals with Decreases)

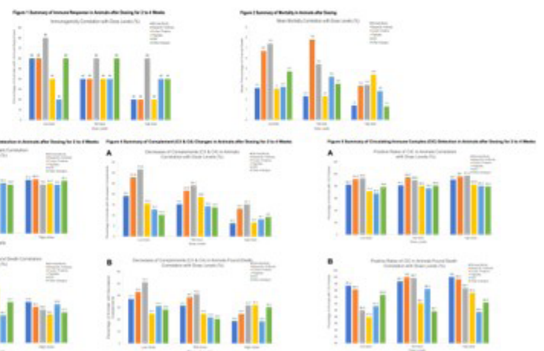
Test Article Types	Number of Studies	Low Dose: $RBC_{\downarrow}$	Low Dose: $HGB_{\downarrow}$	Low Dose: $HCT_{\downarrow}$	Mid-dose: $RBC_{\downarrow}$	Mid-dose: $HGB_{\downarrow}$	Mid-dose: $HCT_{\downarrow}$	High-dose: $RBC_{\downarrow}$	High-dose: $HGB_{\downarrow}$	High-dose: $HCT_{\downarrow}$
Monoantibody	31	8.6	6.2	5.1	9.8	7.8	5.1	14.5	11.5	11.9
Bispecific Antibody	20	18.3	15.4	15.7	20.1	18.4	17.0	30.1	29.1	27.5
Fusion Proteins	13	21.2	17.2	18.2	26.2	25.1	22.8	35.7	33.4	31.5
Peptides	16	6.4	4.1	3.4	10.6	8.2	7.1	12.6	10.8	9.8
ADC	8	10.3	8.6	7.6	9.1	7.6	5.6	11.9	9.1	8.3
Other biologics	34	9.2	7.3	6.1	11.2	8.9	8.3	13.4	11.2	10.1

Table 4 Main Changes of Coagulation Correlating with Dose Levels (% of Animals with Increases)

Test Article Types	Number of Studies	Low Dose: APTT	Low Dose: PT	Low Dose: FIB	Mid-dose: APTT	Mid-dose: PT	Mid-dose: FIB	High-dose: APTT	High-dose: PT	High-dose: FIB
Monoantibody	31	9.2	10.6	6.6	10.7	11.8	9.4	14.6	12.1	17.2
Bispecific Antibody	20	16.3	16.5	12.4	18.4	15.4	16.5	19.6	17.5	22.4
Fusion Proteins	13	20.3	16.2	18.3	25.2	18.2	20.1	28.1	13.2	23.5
Peptides	16	6.7	3.6	4.2	7.9	4.3	8.7	12.6	6.7	16.4
ADC	8	9.2	10.7	7.1	6.2	10.9	10.6	13.1	16.5	13.2
Other biologics	34	8.1	9.2	5.9	7.1	9.8	8.9	10.8	7.4	11.2

Table 5 Main Changes of Clinical Chemistry Correlating with Dose Levels (%of Animals with Changes)

Test Article Types	Number of Studies	Low Dose: $Alb_{\downarrow}$	Low Dose: $A/G_{\downarrow}$	Low Dose: $Glb\uparrow$	Mid-dose: $Alb_{\downarrow}$	Mid-dose: $A/G_{\downarrow}$	Mid-dose: $Glb\uparrow$	High-dose: $Alb_{\downarrow}$	High-dose: $A/G_{\downarrow}$	High-dose: $Glb\uparrow$
Monoantibody	31	11.3	14.2	12.3	8.6	10.7	12.3	10.8	11.6	15.2
Bispecific Antibody	20	18.2	19.6	35.1	17.2	18.5	35.1	19.3	17.2	31.6
Fusion Proteins	13	23.4	26.1	31.4	19.7	24.3	31.4	22.1	24.5	28.3
Peptides	16	8.9	11.7	21.5	11.2	13.2	21.5	10.6	12.1	26.5
ADC	8	11.3	12.7	16.7	10.8	13.4	16.7	8.8	9.3	19.2
Other biologics	34	7.6	8.3	10.4	8.6	9.2	10.4	7.5	7.8	14.7



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