BIOCAD

Изменение подходов к оценке иммуногенности инновационных биологических препаратов при доклинической разработке

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GLP-PLANET IV

Санкт-Петербург

28 – 30 июня 2023 г.

Какая она, иммуногенность в доклинических исследованиях?

3.6. Immunogenicity

Many biotechnology-derived pharmaceuticals intended for human are immunogenic in animals. Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies. Antibody responses should be characterised (e.g., titer, number of responding animals, neutralising or non-neutralising), and their appearance should be correlated with any pharmacological and/or toxicological changes. Specifically, the effects of antibody formation on pharmacokinetic/pharmacodynamic parameters, incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered when interpreting the data. Attention should also be paid to the evaluation of possible pathological changes related to immune complex formation and deposition.

The detection of antibodies should not be the sole criterion for the early termination of a preclinical safety study or modification in the duration of the study design unless the immune response neutralises the pharmacological and/or toxicological effects of the biopharmaceutical in a large proportion of the animals. In most cases, the immune response to biopharmaceuticals is variable, like that observed in humans. If the interpretation of the data from the safety study is not compromised by these issues, then no special significance should be ascribed to the antibody response.

The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Humans may develop serum antibodies against humanised proteins, and frequently the therapeutic response persists in their presence. The occurrence of severe anaphylactic responses to recombinant proteins is rare in humans. In this regard, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are not predictive for reactions in humans; therefore, such studies are considered of little value for the routine evaluation of these types of products.

June 2011
EMA/CHMP/ICH/731268/1998
Committee for medicinal products for human use (CHMP)

ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals

Step 5

Какая она, иммуногенность в доклинических исследованиях?

IV. IMMUNOGENICITY (4)

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies. Such analyses in nonclinical animal studies are not relevant in terms of predicting potential immunogenicity of human or humanized proteins in humans.

Measurement of anti-drug antibodies (ADA) in nonclinical studies should be evaluated when there is:

(1) evidence of altered PD activity;
(2) unexpected changes in exposure in the absence of a PD marker; or
(3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.).

Since it is difficult to predict whether such analysis will be called for prior to completion of the in-life phase of the study, it is often useful to obtain appropriate samples during the course of the study, which can subsequently be analyzed when warranted to aid in interpretation of the study results. When ADAs are detected, their impact on the interpretation of the study results should be assessed (see also section III.F (3.6), paragraph 2 in ICH S6 for further guidance on the impact of immunogenicity).

Characterization of neutralizing potential is warranted when ADAs are detected and there is no PD marker to demonstrate sustained activity in the in vivo toxicology studies. Neutralizing antibody activity can be assessed indirectly with *ex-vivo* bioactivity assay or an appropriate combination of assay formats for PK-PD, or directly in a specific neutralizing antibody assay.

Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2012
ICH

Какая она, иммуногенность в доклинических исследованиях?

- ***Нет прямой трансляции данных иммуногенности с животных на человека***

Интерпретация результатов ФК/ФД и токсичности при проведении ДКИ

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

June 2011
EMA/CHMP/ICH/731268/1998
Committee for medicinal products for human use (CHMP)

ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals
Step 5

Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

Примеры оценки ИГ в доклинических и клинических исследованиях

23 January 2014
EMA/CHMP/71722/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mabthera

International non-proprietary name: RITUXIMAB

Procedure No. EMEA/H/C/000165/X/0083

МАБТЕРА (РИТУКСИМАБ)

Ритуксимаб – химерное анти-CD20 моноклональное антитело

В доклинических (многократное введение) и клинических исследованиях оценивали анти-химерные антитела у обезьян и человека (Monkey Anti–chimeric Antibodies; Human anti-chimeric antibodies HACAs; anti-rituximab antibodies) и анти-человеческие антитела (human anti-human antibodies HAHAs; anti-rHuPH20 antibodies)

17 March 2011
EMA/234266/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Herceptin

(trastuzumab)

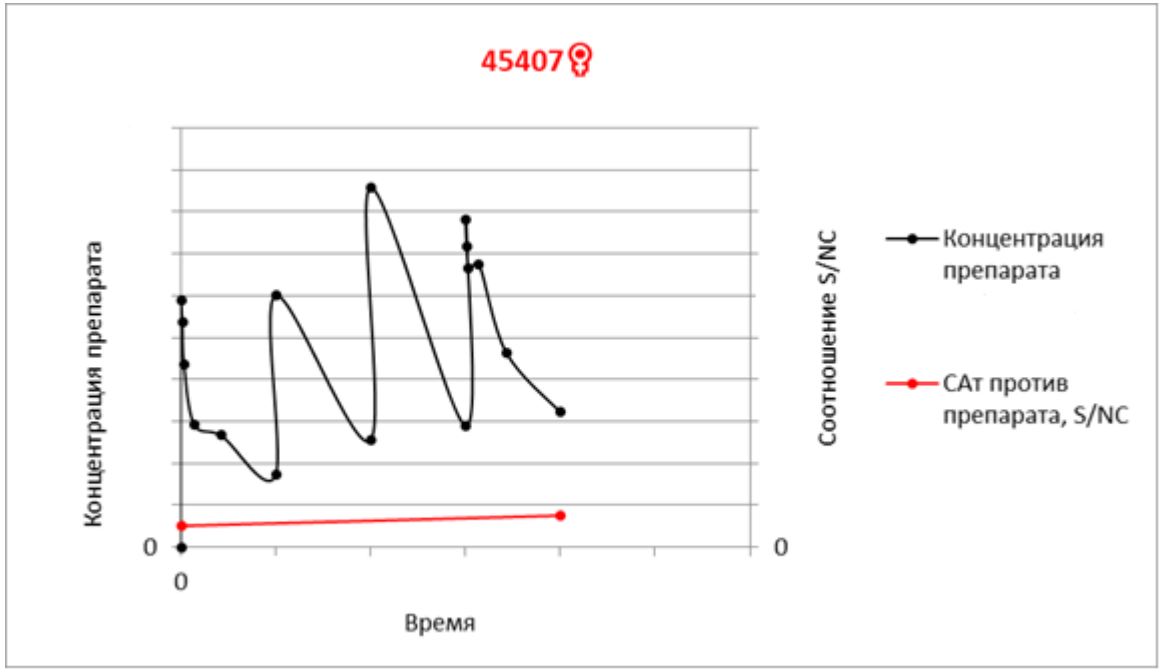
Procedure No.: EMEA/H/C/000278/II/0053

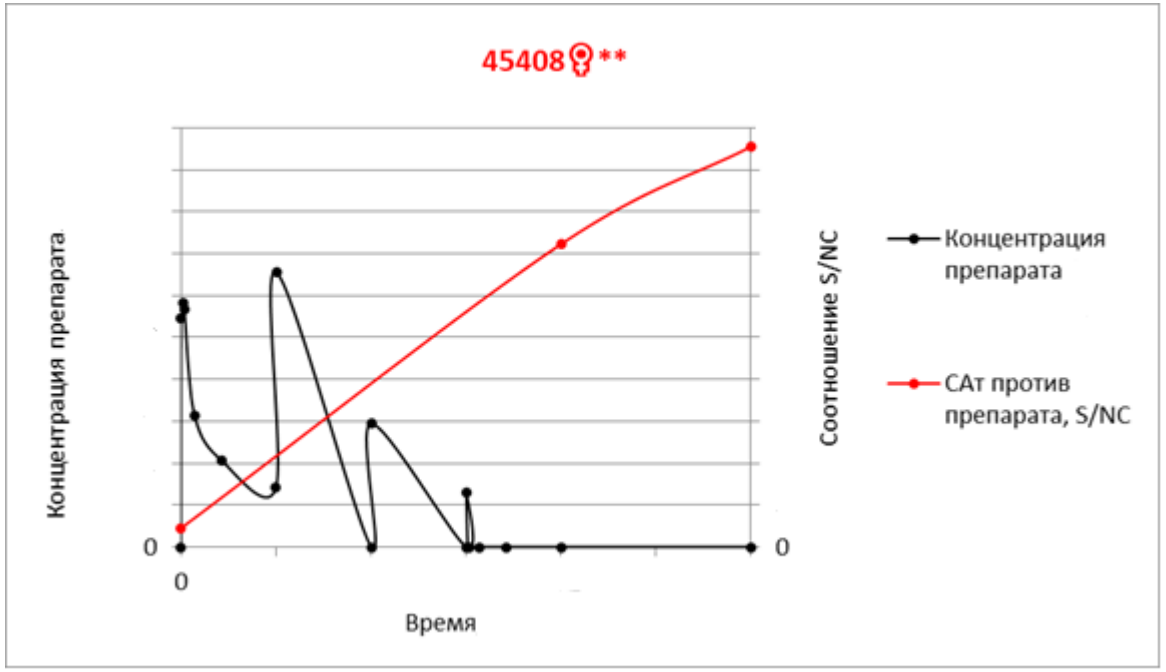
ГЕРЦЕПТИН (ТРАСТУЗУМАБ)

Трастузумаб – химерное моноклональное антитело

Антитела к трастузумабу, в том числе нейтрализующие

Пример изменения ФК профиля препарата





Препарат XXX. В/в введение 1 раз в неделю в течение 4х недель. Точки анализа иммуногенности 0, 4 и 7 неделя.

Roctavian™ (Роктавиан, валоктокоген роксапарвовек) - Генная терапия гемофилии А

- Вектор на основе нереплицирующегося рекомбинантного аденоассоциированного вируса серотипа AAV5, содержащий кДНК части гена фактора свертывания крови VIII (hFVIII-SQ)

ДКИ:

- Мыши CD1 (кровоизлияния!)
- Нечеловекообразные приматы (удлинение АЧТВ)

Анти-AAV5+анти-FVIII антитела

Что еще изменилось?

Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Pharmaceutical Quality/CMC

C. Sensitivity

1. Assay Sensitivity

Assay sensitivity is the lowest concentration at which the antibody preparation consistently produces either a positive result or a readout equal to the cut-point determined for that assay. The assays should have sufficient sensitivity to enable detection of ADA before they reach levels that can be associated with altered pharmacokinetic (PK), pharmacodynamic (PD), safety, or efficacy profiles. Assay sensitivity is assessed using positive control antibody preparations that may not represent the ADA response in a specific subject. For example, positive controls are frequently developed under conditions that enrich for high affinity antibodies. Such high affinity positive controls may overestimate the sensitivity of the assay. Because of this, the assay sensitivity determination contributes to the overall understanding of how the assay performs rather than setting an absolute mass of ADA that will be detected in any given subject. Because the measurement of assay sensitivity can be affected by onboard drug, it is also important to determine assay sensitivity in the presence of the expected concentration of onboard drug (see section IV.C.2).[20] FDA recommends that screening and confirmatory IgG and IgM ADA assays achieve a sensitivity of at least 100 nanograms per milliliter (ng/mL) although a limit of sensitivity greater than 100 ng/mL may be acceptable depending on risk and prior knowledge. Traditionally, FDA has recommended sensitivity of at least 250 to 500 ng/mL. However, recent data suggest that concentrations as low as 100 ng/mL may be associated with clinical events (Plotkin 2010; Zhou et al. 2013). It is understood that neutralization assays may not achieve that level of sensitivity. Assays developed to assess IgE ADA should have sensitivity in the high picograms per milliliter (pg/mL) to low ng/mL range.

Результаты иммуногенности. Метод ACE vs метод Bridge с кислотной диссоциацией

100% иммуногенность во всех группах

Время, недели	ACE						Bridge					
	Наличие антител против BCD-XXX (CAT), группа 1 (мин. доза)						Наличие антител против BCD-XXX (CAT), группа 1 (мин. доза)					
	№ животного, пол						№ животного, пол					
	43197♂	43226♂	43241♂	43236♀	43220♀	43234♀	43197♂	43226♂	43241♂	43236♀	43220♀	43234♀
0	-	-	-	-	-	-	-	-	-	-	-	-
4	+	+	+	-	+	+	-	+	-	-	-	+
8	+	+	+	+	+	+	-	+	+	-	-	+
12	+	+	+	+	+	+	-	+	+	-	-	+
20	+	+	+	+	+	+	-	+	-	-	-	+
26	+	+	+	+	+	+	-	+	-	-	-	+
Время, недели	Наличие антител против BCD-XXX (CAT), группа 2 (средн. доза)						Наличие антител против BCD-XXX (CAT), группа 2 (средн. доза)					
	№ животного, пол						№ животного, пол					
	43227♂	43242♂	43203♂	43237♀	43219♀	43216♀	43227♂	43242♂	43203♂	43237♀	43219♀	43216♀
0	-	-	-	-	+	+	-	-	-	-	-	-
4	+	+	+	+	+	+	-	-	-	-	-	-
8	+	+	+	+	+	+	-	-	-	+	-	-
12	+	+	+	+	+	+	-	-	-	+	-	-
20	+	+	+	+	+	+	-	-	-	+	-	-
26	+	+	+	+	+	+	-	-	-	+	-	-
Время, недели	Наличие антител против BCD-XXX (CAT), группа 3 (макс. доза)						Наличие антител против BCD-XXX (CAT), группа 3 (макс. доза)					
	№ животного, пол						№ животного, пол					
	43225♂	43243♂	43229♂	43232♀	43238♀	43217♀	43225♂	43243♂	43229♂	43232♀	43238♀	43217♀
0	-	-	-	-	-	-	-	-	-	-	-	-
4	+	+	+	+	+	+	-	-	-	-	-	-
8	+	+	+	+	+	+	-	-	-	-	-	-
12	+	+	+	+	+	+	-	-	-	-	-	-
20	+	+	+	+	+	+	-	-	-	-	-	-
26	+	+	+	+	+	+	-	-	-	-	-	-

22,22% иммуногенность в среднем по группам

BIOCAD
Biotechnology Company

Спасибо за внимание!

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