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Commentary

Antibodies against PEGylated enzymes: Treat them with respect!

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Commentary to Gupta et al. "Association of immune response with efficacy and safety outcomes in adults with phenylketonuria administered pegvaliase in phase 3 clinical trials".

Enzyme replacement (ERT) has become a widely used treatment modality in various inborn metabolic disorders. Nevertheless, since the early days of ERT, it has become evident that antidrug antibodies can be induced by the circulating enzyme [1], which can lead to allergic reactions and/or reduced efficacy of the drug in the individual patient [2]. In an effort to "hide" the drug from the immune system, drug designers now often coat the enzyme with polyethylene glycol (PEG) particles in a process called PEGylation. However, within recent years, it has been shown that even PEGylated proteins cannot fully escape the immune system but instead induce anti-PEG antibodies and complement activation [3] in addition to anti-drug antibodies (ADA).

Phenylketonuria (PKU) is a well-known metabolic disorder caused by the deficiency of phenylalanine hydroxylase, the enzyme which catalyzes the conversion of phenylalanine to tyrosine. Up to recent years, low protein dietary treatment and amino acid supplementation were considered the mainstay of therapy, while a certain percentage of patients also responded to BH4 (sapropterin) treatment. However, in a significant proportion of PKU patients, adherence to conventional treatment modalities is poor. Phenylalanine ammonia lyase, an enzyme derived from *Anabaena variabilis*, is cabable to convert phenylalanine to trans-cinnamic acid and ammonia [4]. In a novel strategy, scientists from BioMarin Pharmaceutical Inc. conjugated Phenylalanine ammonia lyase, which was recombinantly produced in *E. coli*, with PEG to increase pharmacodynamic stability and to reduce recognition of the drug by the immune system [5], creating a drug named Pegvaliase (Palynziq™).

In their article of this issue of *EBioMedicine* [6], Gupta et al. give a detailed description of the immune reactions in probands of the PRISM trial [7], who received Pegvaliase for the treatment of PKU. The paper for the first time not only extensively characterizes the specific nature of anti-drug and anti-PEG antibodies in patients treated with a bacterially derived PEGylated enzyme, but also gives an overview of the dynamics of the rise and fall of these specific antibodies.

The authors describe the development of anti-PEG antibodies in the early treatment phase and of anti-PAL antibodies in the later phase of treatment. Early antibody formation was associated with a range of hypersensitivity reactions, requiring careful titration of the dose of the medication. Knowledge of the dynamics of early antibody formation in a large cohort of patients of the reported study should enable the clinicians to develop a personalized dose titration scheme in the individual patients treated with Pegvaliase to avoid severe hypersensitivity reactions and to ensure efficacy of the drug, i.e., reduction of blood Phenylalanine levels. PKU patients, who qualify for this new treatment option, will have to be informed that due to the induction of antibodies a wide range of hypersensitivity reactions can occur in the early phase of treatment with Pegvaliase and that –in contrast to conventional treatment strategies- blood Phe levels will only slowly decrease after starting the new drug treatment. Obviously, in clinical practice, this new treatment option will require close monitoring of efficacy and safety of the drug by the responsible physician, especially in the first months of treatment.

It has to be considered that, with the presence of micro-plastic, i.e. PEG particles, in the food chain and in cosmetics, anti-PEG antibodies are found even in individuals who have never been treated with PEGylated drugs. Do we have to worry about these "constitutive" anti-PEG antibodies as potential modifiers of our immune system or as sensitizers for immunologic reactions against PEGylated drugs? Gupta et al. provide preliminary data to answer this question by showing that the presence of anti-PEG antibodies at baseline did not affect Pegvaliase safety in a subgroup of their PKU probands. However, further research is definitely needed to explore the role of "baseline" anti-PEG antibodies in the general population.

No treatment can exist without any potential side effect. The article by Gupta et al. extensively describes the immunologic reactions associated with a new promising treatment for an old disease, namely PKU. Their study may serve as a template for further studies on the efficacy and safety of PEGylated biologics and as a valuable resource for clinicians, who consider the use of Pegvaliase in their adult PKU patients.

Author contributions

FR wrote this commentary.

Conflicts of Interests

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