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LETTER TO THE EDITOR

Comment on "Adverse Impacts of PEGylated Protein Therapeutics: A Targeted Literature Review"

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Dear Editor,

We read with interest the review article of C.S. Lee et al. on the adverse impacts of polyethylene glycol-conjugated (PEGylated) protein therapeutics [1]. While they raise important considerations regarding safety, immunogenicity, and pharmacokinetics, we believe the discussion could benefit from a more balanced perspective on the established benefits of PEGylation and additional distinctions in interpreting the heterogeneity of PEGylated products. In our own recent review on protein PEGylation, we emphasized that PEGylation techniques have evolved significantly in recent times, resulting in therapeutics with improved pharmacokinetic profiles, reduced immunogenicity, and enhanced patient adherence in many cases [2]. By contrast, the current review draws broad conclusions from a limited set of examples [1]. We caution against extrapolating data from these specific cases to all PEGylated therapeutics [2].

Although the targeted literature review methodology can yield a focused snapshot of adverse events, it inherently omits discussion of the benefits that inform the risk-benefit ratio that is critical to clinical decision-making. Important considerations, such as improving half-life and tolerability, are key to understanding why PEGylation remains widely utilized. Important therapeutic considerations, such as the therapeutic index and expected clinical outcomes, are omitted. These are central to evaluating adverse effects; although all therapeutic products can have adverse effects, the risk–benefit ratio must be examined in the context of the intended therapeutic goal.

The long timescale of the literature search, extending back to the 1990s, dilutes the relevance of findings by failing to account for the impact of significant recent advances in PEGylation techniques and the evolving understanding of PEGylated therapeutic proteins. Despite searching over 30 years (1990–2023), only 29 papers were identified and discussed, some of which are short-term studies offering limited insights into long-term safety, efficacy, and adverse effects. Although 28 PEGylated protein therapeutics were US Food and Drug Administration (FDA)-approved during this time (1990–2023) [3], most results are drawn from studies of the same few drugs approved over a decade ago: peginterferon alfa-2a (40 kDa branched PEG; FDA approval: 2002) [4], peginterferon alfa-2b (12 kDa PEG with bacterial origin; FDA approval: 2001 [Pegintron], 2011 [Sylatron]) [5, 6], pegaspargase (bacterial origin with a large overall PEG size; FDA approval: 1994) [7], and peglotricase (mammalian origin with extensive PEGylation; FDA approval: 2010) [8]. These particular drugs have features that are now well known to affect safety and immunogenicity, including non-human origin and/or extensive PEGylation (such as high molecular weight PEGs or more complex PEG structures) [2]. Different PEGylation methods, such as linear versus branched PEG structures, or variations in molecular weight and conjugation sites, can lead to distinct pharmacokinetic and immunogenicity profiles [2]. The review does not differentiate between these factors, which is essential for a nuanced understanding of the impact of PEGylation. As emphasized in our own review, it is essential to recognize that not all PEGylated therapeutics are the same, and that factors influencing immunogenicity and safety should not be generalized from one therapeutic to another.

Several important details were overlooked in the interpretation of findings. Although the targeted literature review

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scope was limited to human studies with PEGylated proteins, it cites studies on PEGylated liposomes and nanoparticles [9–11], which are not directly comparable and might mislead clinical conclusions on PEGylated proteins. For example, PEGylated liposomes may trigger an immune response, leading to accelerated blood clearance and increased hepatic and splenic drug accumulation during subsequent dosing [2]. This is usually not a concern with PEGylated proteins owing to their different biopharmaceutical properties, and extrapolation of liposome data to proteins could lead to unwarranted caution and incorrect dosing strategies. Furthermore, the adverse events discussed, including infections and hematological, gastrointestinal, and hepatic issues, were mainly reported in patient populations already predisposed to such events (oncology, hepatitis C, and diabetes) [12–15]. In addition, the few studies reviewed may not adequately account for confounding variables such as patient demographics, underlying health conditions, concomitant medications, and dosage differences between PEGylated and non-PEGylated proteins, which can all influence the occurrence and severity of adverse effects. This makes it challenging to tease apart adverse events directly attributed to PEGylation from those attributed to comorbidities or concurrent treatments.

Although anti-PEG antibodies (APAs) can emerge, their clinical impact varies widely depending on titer levels and specific product characteristics. The review does not adequately consider this variability. The evidence used to support the impact of APAs is based primarily on APA prevalence, without considering titers or drug pharmacokinetics, which precludes meaningful assessment of the clinical impact of APAs [13, 16, 17]. For example, recent studies found no pharmacokinetic impact of APAs on pegunigalsidase alfa, likely due to low APA titers [18, 19]. Many patients continue to derive full therapeutic benefit despite the presence of APAs, and, for some therapeutics, dosage adjustments or alternative PEGylation strategies can mitigate any negative effects. Discussions on personalized dosing regimens or alternative PEGylation strategies might further clarify how these products' safety profiles can be optimized in clinical practice.

Overall, we suggest caution in generalizing the conclusions from these limited examples to the broader class of PEGylated protein therapeutics. The safety considerations raised by the authors are valid and warrant ongoing vigilance. However, a more comprehensive and nuanced evaluation, considering recent studies using modern PEGylation techniques, as well as risk mitigation strategies and clinical benefit assessments, would provide a deeper, more balanced perspective on the role of PEGylated protein therapeutics. A systematic literature review approach, as well as including details on how APAs are measured and reported, and discussing analyses that directly compare benefits versus risks of PEGylation in specific clinical scenarios, would provide better assessment of the PEGylated protein landscape. A disproportionate focus on adverse effects, without adequate discussion of risk management, could lead to unnecessary caution among healthcare professionals and patients, potentially discouraging the use of PEGylated therapeutics with well-established safety profiles and clinical benefits. Regulatory bodies may also be influenced by an unbalanced representation, potentially leading to more stringent approval requirements that could hinder innovation in this space. We hope these points help contextualize the review's findings and guide future research toward a better understanding of the complex interplay between PEGylation, immunogenicity, and clinical outcomes.

Declarations

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Conflicts of Interest J. Gonçalves has received consulting fees, payment, or honoraria from AstraZeneca, Celltrion, Chiesi, Pfizer, and Samsung Biologics. He has also received grants or other contracts from AstraZeneca and Pfizer. P. Caliceti declares no conflicts of interest.

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