



Is PEGylation of Drugs Associated with Hypersensitivity Reactions? An Analysis of the Italian National Spontaneous Adverse Drug Reaction Reporting System

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Abstract

Background and objective Evidence highlights the allergenic potential of PEGylated drugs because of the production of anti-polyethylene glycol immunoglobulins. We investigated the risk of hypersensitivity reactions of PEGylated drugs using the Italian spontaneous adverse drug reaction reporting system database.

Methods We selected adverse drug reaction reports attributed to medicinal products containing PEGylated active substances and/or PEGylated liposomes from the Italian Spontaneous Reporting System in the period between its inception and March 2021. As comparators, we extracted adverse drug reaction reports of medicinal products containing the same non-PEGylated active substances and/or non-PEGylated liposomes (or compounds belonging to the same mechanistic class). A descriptive analysis of reports of hypersensitivity reactions was performed. Reporting rates and time to onset of hypersensitivity reactions were also calculated in the period between January 2009 and March 2021. As a measure of disproportionality, we calculated the reporting odds ratio.

Results Overall, 3865 adverse drug reaction reports were related to PEGylated medicinal products and 11,961 to their non-PEGylated comparators. Around two-thirds of patients were female and reports mostly concerned patients aged between 46 and 64 years. The frequency of hypersensitivity reactions reporting was higher among PEGylated versus non-PEGylated medicinal products (11.7% vs 9.4%, $p < 0.0001$). The hypersensitivity reaction reporting rates were higher for PEGylated medicinal products versus non-PEGylated medicinal products, with reporting rate ratios that ranged from 1.4 (95% confidence interval 0.8–2.5) for pegfilgrastim versus filgrastim to 20.0 (95% confidence interval 2.8–143.5) for peginterferon alpha-2a versus interferon alpha-2a. The median time to onset of hypersensitivity reactions was 10 days (interquartile range: 0–61) for PEGylated medicinal products, and 36 days (interquartile range: 3–216) for non-PEGylated comparators. Statistically significant reporting odds ratios were observed when comparing the reporting of hypersensitivity reactions for PEGylated versus non-PEGylated medicinal products (reporting odds ratio: 1.3; 95% confidence interval 1.1–1.4). However, when using all other drugs as comparators, the disproportionality analysis showed no association with hypersensitivity reactions for PEGylated nor non-PEGylated medicinal products, thus suggesting that many other triggers of drug-induced hypersensitivity reactions play a major role.

Conclusions The findings of this analysis of the Italian spontaneous adverse drug reaction database suggest a potential involvement for PEGylation in triggering drug-related hypersensitivity reactions, especially clinically relevant reactions. However, when comparing both PEGylated and non-PEGylated drugs under study to all other drugs no disproportionate reporting of hypersensitivity reactions was observed, probably due to a masking effect owing to the presence in the same database of other medicinal products increasing the threshold required to highlight a safety signal when the entire database is used as a reference.

Extended author information available on the last page of the article

Key Points

Evidence highlights the allergenic potential of PEGylated drugs because of the production of anti-PEG immunoglobulins.

The findings of this study suggest a potential involvement for PEGylation in triggering drug-related hypersensitivity reactions, especially clinically relevant ones.

Anti-PEG antibodies screening is important to identify patients who may require a PEGylated drug with a reduced dosing strategy or the use of non-PEGylated drugs.

1 Introduction

PEGylation is a widely used procedure consisting of the chemical conjugation of one or more molecules of polyethylene glycol (PEG) to a pharmacologically active compound with the main purpose of increasing its half-life [1, 2]. Polyethylene glycol moieties can be conjugated to poorly bioavailable compounds such as peptides, proteins, or nucleic acids as well as to the surface of nanocarriers (mainly lipid nanoparticles). The latter are increasingly being exploited to improve the pharmacokinetic and pharmacodynamic profiles of many drugs with poor biopharmaceutical properties allowing an improvement in the therapeutic index while providing organ and tissue targeting. Concerning nanotechnologies, PEG is used to prevent opsonization and to reduce the clearance of the nanocarriers by the reticuloendothelial system. In this case, PEG is linked to the nanocarrier surface as methoxy-PEG and only PEG2000 is used, as it was the most effective polymer based on experimental data [1].

As the number of PEGylated products on the market increases, safety concerns about the immunogenicity of PEG are rising in the scientific community, as recent evidence highlighted the allergenic potential of PEGylated drugs as a result of the production of anti-PEG immunoglobulins (IgG and IgE [3–5], triggering IgE- or complement-mediated hypersensitivity. In particular, the immunogenic potential of PEG may increase with increasing molecular weight and plasma concentrations [6, 7]. Sellaturay et al. reported a series of five cases of confirmed PEG-induced drug allergies (four cases of anaphylaxis and one case of a systemic allergic reaction) and concluded that the amount of PEG ingested as well as its molecular weight are important factors determining whether an allergic reaction occurs [7].

Anti-PEG antibodies have been detected also in patients who have never been exposed to PEGylated medicinal products, as PEG is present in many products such as toothpaste, shampoo, and detergent. Nevertheless, the titration of anti-PEG antibodies in the blood was not correlated to the activation of an immune response following the administration of PEGylated lipid nanoparticles [8].

The potential immunogenicity of PEGylated drugs is not clearly understood, and it is currently of particular interest as the first COVID-19 vaccines authorized for emergency use in the USA and in the European Union (Comirnaty and Spikevax) are based on PEGylated lipid nanoparticles. These are used to entrap and deliver a messenger RNA (mRNA) strand that, once introduced into the host cells, leads to the synthesis of the spike protein and to the activation of the immune response with the production of anti-spike antibodies. Lipid nanoparticles are vectors of choice for in vivo mRNA delivery [9]. Indeed, they protect the mRNA against degradation, can be easily synthesized in a scalable manner, can be targeted to the specific cell types, and facilitate endosomal escape.

As this technology has never been used for marketed vaccines in the pre-COVID-19 era, a safety concern about the potentially increased risk of allergic reactions to these vaccines has been raised. It has been hypothesized that some patients who have been vaccinated with mRNA vaccines, and already had anti-PEG antibodies, underwent anaphylactic reactions after the administration of those vaccines [10]. Post-marketing observational studies suggested that mRNA vaccines may be associated with an increased risk of severe allergic reactions as compared with conventional vaccines (11.1 vs 1.4 cases per million doses administered, respectively) [11]. In detail, the risk of an allergy after vaccination with an mRNA COVID-19 vaccine appeared to be increased in subjects with a history of allergies [12, 13]. Therefore, we analyzed the spontaneous reports of hypersensitivity adverse reactions (including anaphylactic shock) related to PEGylated drugs with the ultimate goal to explore the role of PEGylation on the drug-related allergy.

Specifically, the aims of this retrospective study were to assess the pattern, frequency, and characteristics (e.g., time to onset, severity, risk factors) of suspected hypersensitivity reactions associated with PEG-containing versus PEG-free active substances in the Italian Spontaneous Reporting System (SRS) and to evaluate the role of PEGylation in triggering drug-induced hypersensitivity reactions by carrying out a disproportionality analysis for both PEGylated and non-PEGylated medicinal products. In addition, we performed the same analyses for drugs delivered based on “Stealth®” nanotechnologies (e.g., liposomes), which are PEGylated or not.

2 Methods

2.1 Data Source

The Italian SRS database (Rete Nazionale di Farmacovigilanza) is a national pharmacovigilance database managed by the Italian Medicines Agency since 2001. Spontaneous and solicited reports of adverse drug reactions (ADRs) are transmitted by healthcare professionals and patients to local pharmacovigilance representatives in a hard copy form or through a web-based system and included into the Rete Nazionale di Farmacovigilanza after a consistency evaluation. Data extraction was carried out using *VigiSegn* (Version 3.0.0), a data warehousing system developed to analyze data from the SRS [14]. Drugs potentially implicated in ADRs are coded according to the Anatomical Therapeutic Chemical classification and suspected ADRs are categorized according to the *Medical Dictionary for Regulatory Activities* (Version 23.0) terminology [15]. Aggregated data concerning the exposure to the included medicinal products during the period between January 2009 (earliest available date for drug consumption data) and March 2021 were provided by the National Observatory on the Use of Medicines of the Italian Medicines Agency, which monitors the consumption and expenditure of medicines supplied by the National Health Service for both outpatient and inpatient assistance.

2.2 Study Drugs

We compiled a list of medicinal products currently marketed in Italy containing PEGylated (PEG+) active substances and/or PEGylated liposomes. To identify PEG+ medicinal products, the European public assessment reports of all the approved drugs in Europe were searched in the European Medicines Agency website as well as in the Italian Medicines Agency website. In addition, a thorough search of the scientific literature was also carried out.

As comparators, we selected medicinal products containing the same non-PEGylated (PEG-) active substances (if not available, compounds belonging to the same mechanistic class were identified) and, with regard to stealth nanoparticles, the same medicinal products containing non-PEGylated liposomal formulations. The PEG+/PEG- medicinal products for each active substance are shown in the Electronic Supplementary Material (ESM).

Spontaneous reports of hypersensitivity reactions related to PEG+/PEG- medicinal products received from the database inception to 31 March, 2021 (date of the last data drawn) were selected. Descriptive and frequency analyses were conducted to compare reports including hypersensitivity adverse reactions related to PEG+ medicinal products versus the corresponding non-PEGylated comparators.

2.3 Study Outcomes

Suspected events of interest were identified by using the Standardized MedDRA Query (SMQ) "Hypersensitivity". Standardized MedDRA Queries include several preferred terms (PTs) referring to a range of clinical conditions, including well-defined diseases and symptoms.

As a subgroup analysis, we also evaluated the events identified by using the SMQ "Anaphylactic reaction", whose PTs are also included in the SMQ "Hypersensitivity". As SMQs are available as narrow or broad searches, we considered the specific narrow scope search [15].

We also specifically explored serious hypersensitivity reactions that were identified as those that: (i) led to death; or (ii) were life threatening; (iii) required hospitalization or prolongation of hospital stay; (iv) caused serious/permanent disability or (v) other clinically relevant conditions; or (vi) caused a congenital anomaly or birth defect [16].

2.4 Statistical Analysis

As a first step, to identify any temporal trend of adverse reactions of interest, the yearly frequency of reports of drug- and vaccine-related hypersensitivity and anaphylactic reactions collected in the Italian SRS database between 2001 and 2020 was assessed and represented with a line plot. Then, a descriptive analysis of patients' age and sex, type of reporter, ADR seriousness and outcomes distribution for all the ADR reports, and specifically for hypersensitivity reactions of the PEG+/PEG- drugs under investigation was carried out. Data for continuous and categorical variables were respectively reported as median, along with interquartile range, and as absolute and relative frequency (percentages). Comparison of subjects' characteristics between two defined groups (e.g., PEG+ vs PEG- medicinal products) was performed by the Mann-Whitney U test and by the Pearson Chi-square test for continuous and categorical variables, respectively.

The frequency of both serious and non-serious hypersensitivity reaction reports, comparing PEG+ with PEG- medicinal products, was assessed. As a subgroup analysis, we also evaluated the frequency of anaphylactic reactions, specifically.

Furthermore, to take into account the different uptake of the medicinal products included in the analyses, we estimated the reporting rates of hypersensitivity reactions, along with their 95% confidence intervals (CIs), in the period between January 2009 (earliest available date for drug consumption data) and March 2021. Reporting rates of hypersensitivity reactions for single PEG+/PEG- medicinal products were calculated by dividing the number of reports collected by drug consumption (expressed per 100,000 dispensed packages) in the same observation period. Reporting rate ratios, along with 95% CIs computed using the Poisson

model, were calculated by comparing the reporting rates of PEG+ versus PEG– medicinal products.

To better evaluate the role of PEGylation in the context of a drug-induced hypersensitivity reaction, for both PEG+ and PEG– medicinal products, the crude reporting odds ratios (RORs), along with 95% CIs, were calculated as a measure of a signal of hypersensitivity reaction (i.e., cases) disproportionate reporting. This quantitative approach is based on the measurement of the frequency of drug-reaction pairs compared with distributions of all other ADRs (i.e., non-cases) from the whole database (excluding vaccines) reported in the same period. Reporting odds ratios were also calculated by comparing the frequency of hypersensitivity reactions reporting among each PEG+ (i.e., index drugs) versus PEG– (i.e., reference drugs) medicinal products. The statistical threshold to identify potential signals of disproportionate reporting was defined as the lower bound of the 95% CIs of the ROR of >1 in the presence of three or more reports [17].

For each medicinal product under investigation, the time to onset of hypersensitivity reports was also calculated as the number of days elapsed between the beginning of drug treatment and the onset of this adverse reaction. Furthermore, to assess the relationship between the proportion (i.e., frequency) of hypersensitivity reactions out of the total ADR reports for the study drugs injected subcutaneously and their PEG size, both bar plots and logistic regression models, which included the PEG size both as continuous and categorical covariates, were performed, separately. Frequencies were reported into the plot with error bars, which denoted a 95% CI computed following the Clopper–Pearson method for binomial CIs.

A p -value <0.05 was set up as the threshold for the statistical significance. All statistical analyses were performed using SAS Release 9.4 (SAS Institute, Cary, NC, USA). Plots were produced using R Foundation for Statistical Computing (R Development Core Team 2008, Vienna, Austria, Version 4.0.3, packages: *ggplot2*, *ggpubr*).

3 Results

The reporting trend of hypersensitivity and anaphylactic reactions in Italy showed that the yearly frequency of both drug- and vaccine-related anaphylactic reaction reporting in the Italian SRS database was constant from 2001 to 2020, while the trend of drug-related hypersensitivity reactions decreased from 35.8% in 2001 to 15.3% in 2020. The yearly frequency of vaccine-related hypersensitivity reactions remained almost constant during the study period, with a peak in 2015 (ESM).

Overall, 608,082 reports were collected in the Italian SRS from its inception to 31 March, 2021 and 172,066 (28.3%)

of them concerned hypersensitivity reactions. The PEG+ medicinal products under investigation accounted for 3865 (0.6%) ADR reports, 451 (11.7%) of which were hypersensitivity reactions, while the PEG– medicinal products accounted for 11,961 (2.0%) ADR reports, 1129 (9.4%) of which reported hypersensitivity reactions.

Table 1 shows the main characteristics of all ADR reports, and of reports of hypersensitivity reactions specifically, related to PEG+/PEG– medicinal products. Concerning both overall ADRs and hypersensitivity reaction reports, around two-thirds of patients were female and they mostly concerned patients aged between 46 and 64 years ($p < 0.0001$ for each comparison), with similar frequencies between PEG+ and PEG– medicinal products. In both cases, the majority of ADRs were reported by physicians, especially for PEG+ versus PEG– medicinal products ($p < 0.0001$ for each comparison), and higher proportions of ADRs reported by patients or non-healthcare professionals (e.g., lawyers, pharmaceutical companies) were observed for PEG– versus PEG+ medicinal products ($p < 0.0001$ for each comparison). The proportion of serious ADRs was higher for PEG+ than for PEG– medicinal products (33.1% vs 23.6%; $p < 0.0001$) and, in particular, the proportion of serious hypersensitivity reaction reports was two times higher for PEG+ than for PEG– medicinal products (33.0% vs 16.3%, respectively; $p < 0.0001$). Regarding ADR outcomes, higher proportions of complete recovery were observed for PEG+ vs PEG– medicinal products, also when focusing on hypersensitivity reactions separately ($p < 0.0001$ for each comparison) (Table 1).

Overall, the frequency of anaphylactic reaction reports among the medicinal products under investigation was very low and they were mostly reported for PEG+ [$N = 20$ (0.5%); minimum–maximum range: 0.1–7.1%] vs PEG– medicinal products [$N = 10$ (0.1%); minimum–maximum range: 0.1–4.5%]. Among PEG+ medicinal products, anaphylactic reactions were mostly reported for liposomal doxorubicin ($N = 8$; 40%) and pegaspargase ($N = 4$; 20%) (Table 2).

Hypersensitivity reactions were more frequently reported for PEG+ versus PEG– medicinal products (11.7% vs 9.4%; $p < 0.0001$) but the frequency of hypersensitivity reactions reporting was significantly higher only for peginterferon alpha-2b, peginterferon beta-1a, certolizumab pegol, pegvisomant, pegaspargase, and PEGylated liposomal doxorubicin as compared with their respective PEG– comparators ($p < 0.0001$ for each comparison). Furthermore, a higher proportion of serious hypersensitivity reactions was observed for all PEG+ versus PEG– medicinal products, except for lipegfilgrastim versus filgrastim, peginterferon beta-1a versus recombinant interferon beta-1b, and methoxy-PEG epoetin beta versus darbepoetin alpha ($p < 0.0001$ for each comparison) (Table 2).

Table 1 Characteristics of the reports of all suspected ADRs and of hypersensitivity reactions specifically associated with PEG+/PEG- active substances in the Italian spontaneous reporting system

Characteristics	Overall			Hypersensitivity reactions		
	PEG+ medicinal products, <i>N</i> = 3865 (%)	PEG- medicinal products, <i>N</i> = 11,961(%)	<i>p</i> value	PEG+ medicinal products, <i>N</i> = 451 (%)	PEG- medicinal products, <i>N</i> = 1129 (%)	<i>p</i> value
Sex						
Female	2385 (61.7)	7493 (62.6)	0.9426	295 (65.4)	776 (68.7)	0.182
Male	1371 (35.5)	4331 (36.2)	0.9426	148 (32.8)	334 (29.6)	0.182
Missing values	109 (2.8)	137 (1.2)	<0.0001	8 (1.8)	19 (1.7)	0.3225
Median age [IQR: Q1–Q3]	53 [44–63]	50 [37–62]	0.0075	53 [44–63]	50 [38–63]	0.0066
Age groups (years)						
<18	42 (1.1)	652 (5.5)	<0.0001	14 (3.1)	51 (4.5)	0.1936
18–45	1030 (26.6)	3546 (29.6)	<0.0001	107 (23.8)	346 (30.6)	0.0048
46–64	1837 (47.5)	4156 (34.7)	<0.0001	218 (48.3)	397 (35.2)	<0.0001
65–80	693 (17.9)	1674 (14.0)	0.0001	88 (19.5)	166 (14.7)	0.0218
>80	27 (0.7)	201 (1.7)	<0.0001	2 (0.4)	40 (3.5)	0.0005
Missing value	236 (6.2)	1732 (14.5)	<0.0001	22 (4.9)	129 (11.4)	0.0002
Type of reporter						
Physician ^a	2769 (71.6)	6187 (51.7)	<0.0001	350 (77.6)	661 (58.5)	<0.0001
Pharmacist	302 (7.8)	1150 (9.6)	0.0005	33 (7.4)	123 (10.9)	0.0286
Other healthcare professional ^b	585 (15.1)	1457 (12.2)	<0.0001	43 (9.5)	124 (11.0)	0.3759
Patient/non-healthcare professional ^c	208 (5.4)	3165 (26.5)	<0.0001	25 (5.5)	221 (19.6)	<0.0001
Missing value	1 (0.0)	2 (0.0)	0.7234	0 (0.0)	0 (0.0)	–
Seriousness						
Not serious	2456 (63.5)	8083 (67.6)	<0.0001	289 (64.1)	850 (75.3)	<0.0001
Missing value	129 (3.3)	1061 (8.9)	<0.0001	13 (2.9)	95 (8.4)	<0.0001
Serious	1280 (33.1)	2817 (23.6)	<0.0001	149 (33.0)	184 (16.3)	<0.0001
Hospitalization/prolonged hospital stay ^d	522 (40.8)	1104 (39.2)	0.3305	47 (31.5)	67 (36.4)	0.3518
Other clinically relevant condition ^d	605 (47.3)	1431 (50.8)	0.0273	76 (51.0)	97 (52.7)	0.756
Life-threatening ^d	90 (7.0)	140 (5.0)	0.0089	24 (16.2)	15 (8.1)	0.0248
Serious or permanent disability ^d	37 (2.9)	61 (2.2)	0.1672	2 (1.3)	3 (1.6)	0.8298
Death ^d	25 (1.9)	75 (2.7)	0.355	0 (0.0)	2 (1.2)	0.2018
Congenital anomalies ^d	1 (0.1)	6 (0.2)	0.3298	0 (0.0)	0 (0.0)	–
Outcome of ADR						
Complete recovery	1691 (43.8)	3271 (27.3)	<0.0001	249 (55.2)	461 (40.8)	<0.0001
Improvement	846 (21.9)	1713 (14.3)	0.0049	95 (21.1)	191 (16.9)	0.0609
Not yet recovered	450 (11.6)	1635 (13.7)	<0.0001	33 (7.3)	125 (11.1)	0.0224
Recovery with sequelae	74 (1.9)	239 (2.0)	0.0049	3 (0.7)	23 (2.0)	0.0513
Death	27 (0.7)	103 (0.9)	0.0367	0 (0.0)	4 (0.4)	0.2041
Missing value	777 (20.1)	5000 (41.8)	<0.0001	71 (15.7)	325 (28.8)	<0.0001

ADR adverse drug reaction, IQR interquartile range, PEG polyethylene glycol

^aHospital doctors, general practitioners, family pediatricians, specialists

^bNurses, dentists, poison centers

^cLawyers, pharmaceutical companies

^dProportions calculated on the total of serious ADRs

Table 2 Frequency of hypersensitivity reactions and anaphylactic shock for PEG+ (including liposomal formulations) versus PEG– medicinal products in the Italian spontaneous reporting system database

PEG	Active substance (total number of reports)	Hypersensitivity reactions, <i>N</i> (%)		Anaphylactic shock, <i>N</i> (%)
		Total, <i>N</i> (%)	Serious ADRs, <i>N</i> (%)	Total, <i>N</i> (%)
+	Pegvisomant (<i>N</i> = 51)	5 (9.8)	2 (3.9)	0 (0.0)
–	Somatropin (<i>N</i> = 731)	35 (4.8)	3 (0.4)	0 (0.0)
+	Pegaspargase (<i>N</i> = 56)	21 (37.5)	11 (19.6)	4 (7.1)
–	Asparaginase (<i>N</i> = 2)	0 (0.0)	0 (0.0)	0 (0.0)
+	Peginterferon alpha-2b (<i>N</i> = 694)	54 (7.8)	12 (1.7)	0 (0.0)
–	Interferon alpha-2b (<i>N</i> = 266)	19 (7.1)	2 (0.8)	0 (0.0)
+	Pegfilgrastim (<i>N</i> = 164)	15 (9.1)	8 (4.9)	2 (1.2)
	Lipegfilgrastim (<i>N</i> = 61)	5 (8.2)	1 (1.6)	1 (1.6)
–	Filgrastim (<i>N</i> = 795)	134 (16.8)	34 (4.3)	1 (0.1)
+	Peginterferon beta-1a (<i>N</i> = 579)	54 (9.3)	4 (0.7)	1 (0.2)
–	Interferon beta-1a (<i>N</i> = 3111)	204 (6.6)	16 (0.5)	0 (0.0)
	Recombinant interferon beta-1b (<i>N</i> = 547)	50 (13.5)	6 (1.1)	0 (0.0)
+	Methoxy-PEG epoetin beta (<i>N</i> = 21)	3 (14.3)	1 (4.8)	1 (4.8)
–	Epoetin alpha (<i>N</i> = 381)	54 (14.2)	10 (2.6)	0 (0.0)
	Darbepoetin alpha (<i>N</i> = 111)	27 (24.3)	7 (6.3)	1 (0.9)
	Epoetin beta (<i>N</i> = 54)	8 (14.8)	2 (3.7)	0 (0.0)
+	Peginterferon alpha-2a (<i>N</i> = 1099)	99 (9.0)	33 (3.0)	1 (0.1)
–	Interferon alpha-2a (<i>N</i> = 73)	10 (13.7)	1 (1.4)	0 (0.0)
+	Nonacog beta pegol (<i>N</i> = 0)	0 (0.0)	0 (0.0)	0 (0.0)
–	Nonacog alpha (<i>N</i> = 20)	3 (15.0)	3 (15.0)	1 (5.0)
	Nonacog gamma (<i>N</i> = 0)	0 (0.0)	0 (0.0)	0 (0.0)
	Eftrenonacog alpha (<i>N</i> = 2)	0 (0.0)	0 (0.0)	0 (0.0)
	Trenonacog alpha (<i>N</i> = 0)	0 (0.0)	0 (0.0)	0 (0.0)
+	Certolizumab pegol (<i>N</i> = 446)	61 (13.7)	19 (4.3)	2 (0.4)
–	Adalimumab (<i>N</i> = 2673)	258 (9.6)	50 (1.9)	1 (0.04)
	Etanercept (<i>N</i> = 1995)	234 (11.7)	33 (1.7)	4 (0.2)
	Golimumab (<i>N</i> = 596)	51 (8.6)	9 (1.5)	0 (0.0)
<i>Liposomal formulations</i>				
+	Doxorubicin PEGylated liposomal (<i>N</i> = 688)	134 (19.5)	58 (8.4)	8 (1.2)
–	Doxorubicin liposomal (<i>N</i> = 271)	14 (5.2)	4 (1.5)	0 (0.0)
+	Irinotecan PEGylated liposomal (<i>N</i> = 6)	0 (0.0)	0 (0.0)	0 (0.0)
–	Irinotecan (<i>N</i> = 333)	28 (8.4)	4 (1.2)	2 (0.6)

ADRs adverse drug reactions, IQR interquartile range, PEG polyethylene glycol, + PEGylated medicinal product, – non-PEGylated medicinal product, RNF Rete Nazionale di Farmacovigilanza
Evaluated till 31 March, 2021

In the period between January 2009 and March 2021, the hypersensitivity reaction reporting rates were higher for PEG+ versus PEG– medicinal products, with reporting rate ratios that ranged from 1.4 (95% CI 0.8–2.5) for pegfilgrastim versus filgrastim to 20.0 (95% CI 2.8–143.5) for peginterferon alpha-2a versus interferon alpha-2a (Table 3).

Statistically significant RORs were observed when comparing the reporting of both serious [ROR: 2.5 (95% CI 2.0–3.2)] and non-serious [ROR: 1.3 (95% CI 1.1–1.4)] hypersensitivity reactions for PEG+ versus PEG– medicinal products. However, when using all other drugs as

comparators, the disproportionality analysis showed no association with hypersensitivity reactions for PEG+ nor PEG– medicinal products (Table 4).

The median time to onset of hypersensitivity reactions was 10 (interquartile range: 0–61) days for PEGylated medicinal products, and 36 (interquartile range: 3–216) days for non-PEGylated comparators (Table 5). No statistically significant association between the frequency of hypersensitivity reaction reporting and increasing PEG molecular weight of medicinal products administered subcutaneously was found, as reported in the bar plots in Fig. 1.

Table 3 RRs and RRRs of hypersensitivity reactions per 100,000 packages dispensed of both PEGylated and non-PEGylated medicinal products, during the period January 2009–March 2021

PEG+ medicinal products		PEG– medicinal products		RRR
Active substance	Hypersensitivity RR per 100,000 (95% CI)	Active substance	Hypersensitivity RR per 100,000 (95% CI)	
Pegvisomant	5.3 (2–13.5)	Somatropin	0.7 (0.5–1.1)	7.2 (2.5–20.3)
Pegaspargase	298.8 (195.5–456.3)	Asparaginase	0.0 (0.0–0.0)	N.A.
Peginterferon alpha-2b	5.3 (3.9–7.2)	Interferon alpha-2b	0.3 (0.1–1.6)	18.2 (2.5–132.6)
Pegfilgrastim	1.9 (1.1–3.2)	Filgrastim	1.4 (1.1–1.6)	1.4 (0.8–2.5)
Lipegfilgrastim	7.1 (3.0–16.7)			5.3 (2.2–12.9)
Peginterferon beta-1a	35.7 (27.4–46.6)	Interferon beta-1a	9.5 (8.3–10.9)	3.8 (2.8–5.1)
		Interferon beta-1b	12.5 (9.5–16.6)	2.9 (1.9–4.2)
Methoxy-PEG epoetin beta	0.4 (0.1–1.2)	Epoetin alpha	0.1 (0.1–0.2)	3.1 (1.0–9.9)
		Darbepoetin alpha	0.1 (0.1–0.2)	2.9 (0.9–9.7)
		Epoetin beta	0.03 (0.0–0.1)	12.5 (2.8–55.7)
Peginterferon alpha-2a	3.9 (3.2–4.9)	Interferon alpha-2a	0.2 (0–1.1)	20.0 (2.8–143.5)
Nonacog beta pegol	0.0 (0.0–0.0)	Nonacog alpha	1.0 (0.3–2.8)	N.A.
		Nonacog gamma	0.0 (0.0–0.0)	N.A.
		Eftrenonacog alpha	0.0 (0.0–0.0)	N.A.
Certolizumab pegol	17.8 (13.9–22.9)	Adalimumab	8.9 (7.9–10.1)	2.0 (1.5–2.6)
		Etanercept	8.1 (7–9.3)	2.2 (1.7–2.9)
		Golimumab	8.6 (6.6–11.3)	2.1 (1.4–3.0)
<i>Liposomal formulations</i>				
Doxorubicin PEGylated liposomal	25.7 (21.5–30.7)	Doxorubicin liposomal	12.2 (7.3–20.4)	2.1 (1.2–3.6)
Irinotecan PEGylated liposomal	0.0 (0.0–0.0)	Irinotecan	4.7 (3.2–7.0)	N.A.

CI confidence interval, N.A. not applicable, PEG polyethylene glycol, + PEGylated medicinal product, – non-PEGylated medicinal product, RR reporting rate, RRR reporting rate ratio

4 Discussion

To our knowledge, this is the first study that explored the role of PEGylation in triggering hypersensitivity reactions using the Italian SRS database. In line with a recent Italian pharmacovigilance study, our analysis showed that drug-induced hypersensitivity reactions were mostly reported in female patients aged more than 40 years [18].

This study showed a disproportionate reporting of hypersensitivity reactions for most PEG+ medicinal products, i.e., peginterferon alpha-2b, peginterferon beta-1a, certolizumab pegol, pegvisomant, pegaspargase, and PEGylated liposomal doxorubicin, versus their respective PEG– comparators. However, when using all other drugs as comparators, no disproportionate reporting of hypersensitivity reactions for PEG+/PEG– medicinal product was observed. This may be due to a masking effect, owing to the presence of other medicinal products (e.g., antibiotics, other antineoplastic agents, and anti-inflammatory drugs) in the same database, which increase the threshold required for highlighting a signal [19].

A number of studies and clinical reports showed that PEG administration may be associated with moderate-to-severe

hypersensitivity reactions, mainly due to complement system activation [4, 20] (complement activation-related pseudo allergy) or to the production of anti-PEG antibodies that may lead to an acceleration of the blood clearance (ABC phenomenon) of the PEGylated drug, resulting in efficacy loss and hypersensitivity reactions [21–23].

Many of the reported hypersensitivity reactions, mainly for PEG– medicinal products, had very long median times to onset. Indeed, the SMQ “hypersensitivity” does not only contain PTs pointing towards immediate hypersensitivity, but also PTs pertaining to delayed hypersensitivity (e.g., cutaneous adverse reactions). As a confirmation of this, most of the reports of hypersensitivity reactions for the medicinal products under investigation, especially those judged as serious, were cutaneous reactions.

Cutaneous hypersensitivity reactions have been frequently reported for interferons, and for peginterferon alpha-2b especially, and they have been extensively described in the literature [24–29]. A large body of evidence suggests that cutaneous hypersensitivity reactions are more frequent for peginterferon alpha as compared with its non-PEGylated form [28–30] and that switching from peginterferon alpha to conventional interferon alpha

Table 4 Analysis of hypersensitivity reaction disproportionate reporting comparing PEG+ versus PEG– medicinal products, PEG+ medicinal products versus the whole database and PEG– medicinal products versus the whole database

PEG+ medicinal products vs PEG– medicinal products (overall ADRs)				
PEG+ ^a		PEG– ^b		ROR (95% CI)
HSR reports	Other ADR reports	HSR reports	Other ADR reports	
451	3414	1129	10,832	1.3 (1.1–1.4)
PEG+ medicinal products vs PEG– medicinal products (serious ADRs)				
PEG+ ^a		PEG– ^b		ROR (95% CI)
HSR reports	Other ADR reports	HSR reports	Other ADR reports	
149	302	184	945	2.5 (2.0–3.3)
PEG+ medicinal products vs the whole SRS database				
PEG+ ^a		Whole SRS database ^b		ROR (95% CI)
HSR reports	Other ADR reports	HSR reports	Other ADR reports	
451	3414	111,961	393,516	0.5 (0.4–0.5)
PEG– medicinal products vs the whole SRS database				
PEG– ^a		Whole SRS database ^b		ROR (95% CI)
HSR reports	Other ADR reports	HSR reports	Other ADR reports	
1129	10,382	111,283	386,098	0.4 (0.3–0.4)

ADR adverse drug reaction, CI confidence interval, HSR hypersensitivity reaction, PEG+ PEGylated medicinal products, PEG– non-PEGylated medicinal products, ROR reporting odds ratio, SRS spontaneous reporting system

^aIndex drugs

^bReference group

decreases the risk of severe allergic cutaneous reactions [30–32], suggesting that the likely culprit for the skin reaction may be the PEG component of peginterferon [30–32].

Additionally, pegaspargase was significantly associated with an increased reporting of hypersensitivity reactions. Although a large body of evidence proved that it causes less hypersensitivity as compared with asparaginase, its non-PEGylated form [33–36], such a difference could not be found in this study because asparaginase was not widely used in Italy during the study period (overall, only 632 packages were dispensed from 2018 to 2021) and no hypersensitivity reaction with this drug was identified in the Italian SRS.

Hypersensitivity reactions reported for certolizumab pegol mainly concerned cutaneous reactions such as hives and skin rashes. Cutaneous reactions, and psoriasiform skin eruptions in particular, are among the most common adverse reactions of tumor necrosis factor- α inhibitors and a considerable number of case reports describing adverse cutaneous reactions in patients treated with certolizumab have been published [37–41]. It has been proposed that increased levels of interferon- α due to tumor necrosis factor- α suppression and the activation of interleukin-23/T-helper-17 axis may

play a crucial role in the development of such paradoxical reactions [42]. Therefore, cutaneous adverse reactions due to a tumor necrosis factor- α blockade seems to be a class effect.

It was postulated that the interaction between PEG and antibodies is stabilized and then enhanced when PEG is exposed on the surface of nanoparticles, suggesting that PEGylated nanocarriers might be even more immunogenic when compared with PEGylated drugs. This hypothesis seems to be confirmed looking at the data collected for liposomal doxorubicin, which is associated with important adverse events likely caused by complement activation, such as the hand-foot syndrome and infusion-related reactions [43]. As compared with the non-liposomal formulation, PEGylated liposomal doxorubicin is associated also with a wider range of cutaneous adverse reactions, reflecting its pharmacokinetics and tissue distribution [44].

Nevertheless, although a correlation between the presence of antibodies against methoxy-PEG and complement activation upon incubation with liposomal doxorubicin has not been found, the immunogenicity of this formulation is well known, and data drawn from liposomal doxorubicin experience cannot be transferred to other liposomal-based medicinal products. This is further demonstrated by the lack

Table 5 Time-to-onset analysis of hypersensitivity reactions comparing PEGylated active substances and non-PEGylated active substances

PEG	Active substance (<i>N</i> total ADR reports)	Hypersensitivity reactions, <i>N</i> (%)	Median time to onset (days) [IQR]
+	Pegvisomant (<i>N</i> = 51)	5 (9.8)	9 [<1 –28]
–	Somatropin (<i>N</i> = 731)	35 (4.8)	110.5 [2.5–345.5]
+	Pegaspargase (<i>N</i> = 56)	21 (37.5)	<1 [<1 – <1]
–	Asparaginase (<i>N</i> = 2)	0 (0.0)	–
+	Peginterferon alpha-2b (<i>N</i> = 694)	54 (7.8)	28 [13–85]
–	Interferon alpha-2b (<i>N</i> = 266)	19 (7.1)	26 [5–106]
+	Pegfilgrastim (<i>N</i> = 164)	15 (9.1)	<1 [<1 –1]
–	Lipegfilgrastim (<i>N</i> = 61)	5 (8.2)	3.5 [1.5–13.0]
–	Filgrastim (<i>N</i> = 795)	134 (16.8)	1 [<1 –3]
+	Peginterferon beta-1a (<i>N</i> = 579)	54 (9.3)	69 [14–274]
–	Interferon beta-1a (<i>N</i> = 3111)	204 (6.6)	248.5 [22.0–1191.5]
–	Recombinant interferon beta-1b (<i>N</i> = 547)	50 (13.5)	345 [1–885]
+	Methoxy-PEG epoetin beta (<i>N</i> = 21)	3 (10.0)	25.5 [<1 –51.0]
–	Epoetin alpha (<i>N</i> = 381)	54 (14.2)	4.5 [1.0–22.5]
–	Darbepoetin alpha (<i>N</i> = 111)	27 (24.3)	16 [<1 –67]
–	Epoetin beta (<i>N</i> = 54)	8 (14.8)	2.5 [1.0–53.0]
+	Peginterferon alpha-2a (<i>N</i> = 1099)	99 (9.0)	47.5 [13.0–96.0]
–	Interferon alpha-2a (<i>N</i> = 73)	10 (13.7)	35 [4–90]
+	Nonacog beta pegol (<i>N</i> = 0)	0 (0.0)	–
–	Nonacog alpha (<i>N</i> = 20)	3 (15.0)	7 [<1 –14]
–	Nonacog gamma (<i>N</i> = 0)	0 (0.0)	–
–	Eftrenonacog alpha (<i>N</i> = 2)	0 (0.0)	–
–	Trenonacog alpha (<i>N</i> = 0)	0 (0.0)	–
+	Certolizumab pegol (<i>N</i> = 446)	61 (13.7)	15 [<1 –60]
–	Adalimumab (<i>N</i> = 2673)	258 (9.6)	151.5 [16.0–386.0]
–	Golimumab (<i>N</i> = 596)	51 (8.6)	61.0 [14.5–142.5]
–	Etanercept (<i>N</i> = 1995)	234 (11.7)	41.5 [15.0–231.0]
<i>Liposomal formulations</i>			
+	Doxorubicin PEGylated liposomal (<i>N</i> = 688)	134 (19.5)	<1 [<1 –2]
–	Doxorubicin liposomal (<i>N</i> = 271)	14 (5.2)	<1 [<1 –14.5]
+	Irinotecan PEGylated liposomal (<i>N</i> = 6)	0 (0.0)	–
–	Irinotecan (<i>N</i> = 333)	28 (8.4)	49 [3–157]

ADRs adverse drug reactions, IQR interquartile range, PEG polyethylene glycol, + PEGylated medicinal product, – non-PEGylated medicinal product, RNF Rete Nazionale di Farmacovigilanza

Evaluated since 31 March, 2021

of a severe adverse effect registered in the case of PEGylated liposomes carrying irinotecan. In fact, PEG-induced complement activation-related pseudo allergy is dependent on several factors including liposome composition and physicochemical properties, along with the density of the PEG coating, the dose, and the frequency of administration. As an example, the immunogenicity of liposomal doxorubicin is attributed to both the negative charge and the oval shape of liposomes resulting from the crystallization of doxorubicin in the aqueous core. Equivalent formulations having a spherical shape did not lead to an increased complement activation [45]. In general, negatively or positively charged liposomes, with a cholesterol content higher than 45%,

given at a high lipid dose through a slow infusion might be associated with a higher risk of the complement activation-related pseudo allergy phenomenon regardless of the presence of PEG moieties on the surface. As further proof of this, negatively charged non-PEGylated liposomes containing amphotericin B, used for the treatment of fungal infection, were found to increase levels of complement activation to a higher extent with respect to analogous non-charged liposomes [45].

In addition to these considerations, the results of our study are in line with those of a recently published pharmacovigilance study that explored the adverse events potentially associated with PEGylation by comparing

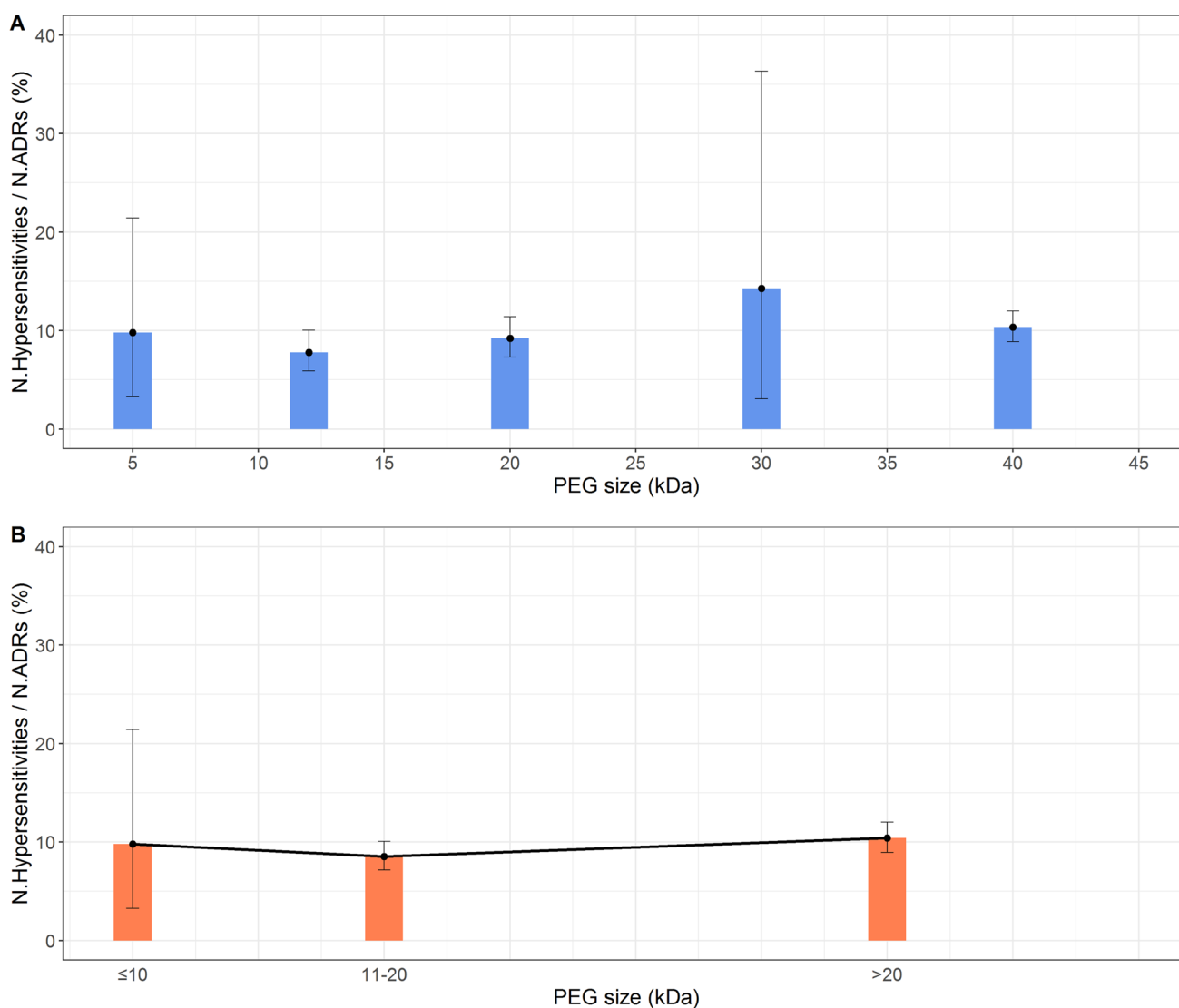


Fig. 1 Proportion of hypersensitivity reaction reports over the total number of adverse drug reactions (ADRs) with respect to ungrouped (A) and grouped (B) polyethylene glycol (PEG) size of PEGylated

medicinal products that are injected subcutaneously. Error bars represent the 95% confidence interval around the computed percentages. *N.* number

ADR reports of PEG+ and PEG– drugs from the US Food and Drug Administration Adverse Event Reporting System database [46]. This study found that three immunogenicity-related PTs (i.e., rash, pruritus, and erythema) and the SMQs of hypersensitivity and anaphylactic reactions were slightly higher for PEGylated medicinal products, with a trend toward statistical significance, thus highlighting the importance of screening for anti-PEG antibodies to identify patients who may require a PEGylated drug with a reduced dosing strategy or the use of non-PEGylated drugs [46].

Furthermore, conflicting evidence exists on the role of PEG size in triggering hypersensitivity reactions [47]. Findings from this study suggest that PEG molecular weight is not statistically associated with an increased frequency of

hypersensitivity reactions reporting; however, such statistical evidence does not necessarily translate into biological evidence, thus suggesting the need to conduct other studies investigating the role of PEG size in triggering hypersensitivity reactions.

The SRS is the cornerstone of pharmacovigilance for post-marketing surveillance of drugs and for the detection of new potential safety signals. In our study, we provided additional evidence concerning PEG-related hypersensitivity. To the best of our knowledge, this is the first pharmacovigilance study calculating the reporting rate of hypersensitivity reactions and to investigate the relationship between the frequency of hypersensitivity reaction reporting and PEG size for each of the medicinal products included in the analyses.

However, some limitations warrant caution. Many of the reports of hypersensitivity reactions for the medicinal products under investigation were long-term cutaneous reactions that were not necessarily due to hypersensitivity and/or allergic mechanisms, consequently accounting for a possible overestimation of the risk. The SRS has several known limitations that should be acknowledged, including under-reporting of suspected ADRs [48], selective over-reporting, missing demographic and clinical data, and a lack of a denominator (i.e., the total number of drug users), which precludes measuring the incidence of hypersensitivity reactions for both PEG+ and PEG– drugs. Furthermore, ROR estimates may also be affected by several biases ascribed to reporting trends in the SRS database. Finally, the analysis of SRS is mainly aimed at generating hypotheses, and causative relationships between the drugs and the studied ADRs can only be surmised. Indeed, drug-induced hypersensitivity reactions may also be due to specific excipients that are known to be involved in such adverse reactions, and delayed hypersensitivity specifically, rather than specific active principles [49]. Moreover, as it was not possible to stratify the analyses by route of administration, we compared drugs with more than one route of administration to drugs with only one route of administration (e.g., peginterferon beta-1a vs interferon beta-1a and pegaspargase vs asparaginase). However, it should be noted that there are no significant differences concerning the frequency of hypersensitivity reactions between the various parenteral routes of administration, but mostly between oral and parenteral routes of administration [50]. As we compared only drugs that are administered through parenteral routes of administration, we think this was unlikely to affect our analysis.

Finally, to really understand the role of PEG in the allergy phenomenon, more PEG+/PEG– liposomes comparators are needed, as lipid nanoparticles can activate the immune system by themselves and, as such, non-liposomal drugs cannot be used as controls in these studies. Therefore, findings from the analysis of the SRS need to be evaluated further through pharmacoepidemiological studies.

5 Conclusions

Most of the hypersensitivity reactions reported for both PEGylated and non-PEGylated medicinal products included in the analyses were cutaneous reactions due to delayed hypersensitivity mechanisms. The findings of this analysis of the Italian spontaneous ADR database suggest a potential involvement for PEGylation in triggering drug-related hypersensitivity reactions, especially clinically relevant reactions. However, when comparing both PEGylated and non-PEGylated drugs under study to all other drugs, there was no disproportionate reporting of hypersensitivity reactions, probably due to a masking

effect, owing to the presence in the same database of other medicinal products increasing the threshold required to highlight a safety signal. Therefore, it is necessary to carry out more real-world studies to better investigate the potential involvement of PEGylation in triggering hypersensitivity reactions.

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Declarations

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Conflict of interest Gianluca Trifirò has served in the last 3 years on advisory boards/seminars funded by SANOFI, Eli Lilly, AstraZeneca, Abbvie, Servier, Mylan, Gilead, and Amgen; he was the scientific director of a Master program on pharmacovigilance, pharmacoepidemiology, and real-world evidence, which has received a non-conditional grant from various pharmaceutical companies; and he coordinated a pharmacoepidemiology team at the University of Messina until October 2020, which has received funding for conducting observational studies from various pharmaceutical companies (Boehringer Ingelheim, Daichii Sankyo, PTC Pharmaceuticals). He is also a scientific coordinator of the academic spin-off “INSPIRE srl”, which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.). None of these listed activities is related to the topic of the article. The other authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article apart from those disclosed.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors contributed equally to this work. All authors read and approved the final version.


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