



Cytokine release reactions to Filgrastim and Pegfilgrastim

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Abstract

Cytokine release reactions to filgrastim and pegfilgrastim may produce anaphylaxis. This is the first biomarker-confirmed case successfully managed with intravenous desensitization, offering a practical and reproducible approach for patients requiring continued G-CSF therapy despite severe hypersensitivity reactions. First documented cytokine release reaction to G-CSF with IL-6 confirmation and successful desensitization protocol.

Keywords: Allergy; Cytokine; G-CSF; Filgrastim; Pegfilgrastim

Introduction

We present the case of a 55-year-old woman in treatment with third-line monthly Teclistamab and exogenous granulocyte colony-stimulating factor (G-CSF) support against a multiple myeloma. Filgrastim 300 mcg was administered weekly for years without incident. However, since June 2024, the patient experienced episodes of profuse sweating, severe abdominal pain with diarrhea, and dyspnea secondary to the pain for approximately 60–90 minutes after each dose. In November 2024, the patient was switched to Pegfilgrastim 6 mg monthly, with identical symptoms after each administration.

Materials and Methods

Allergy testing using skin prick and 1/1000, 1/100 and 1/10 intradermal tests with Filgrastim and Pegfilgrastim

were negative (1,2), therefore, a subcutaneous challenge with Pegfilgrastim 6 mg was performed. Approximately 10 minutes after the challenge test, the patient developed severe abdominal pain with nausea and diarrhea, nasal congestion, conjunctival hyperemia, watery nose, and dyspneic cough. Adrenaline 0.3 ml intramuscularly was administered with methylprednisolone 40 mg, dexchlorpheniramine 6 mg, paracetamol 1 g, and metoclopramide 1 g intravenously. 5.34 µg/L tryptase and 25.8 pg/mL interleukin-6 were objectified 1 hour after the reaction (baseline tryptase 4.12 and interleukin-6 levels of <1.5 pg/mL). The patient's diagnosis was cytokine release reactions to Filgrastim and Pegfilgrastim. A 12-step intravenous desensitization protocol (3) with home premedication (Montelukast, Ebastine, Acetyl Salicylic Acid, Famotidine and Diazepam) was performed with good tolerance and allowed a conventional administration of a subcutaneous booster

dose 24 hours after desensitization. Since April 2025, Filgrastim has been administered weekly in an 8-step intravenous desensitization

protocol (Table 1) with a subcutaneous booster dose 24 hours after desensitization, without incident.

Table 1: 8-step intravenous desensitization protocol.

Step	Solution	Rate (ml/h)	Time (minutes)	Administered dose (mcg)	Cumulative dose (mcg)
1	A	0.1	15	0.37	0.37
2	A	0.2	15	0.75	1.125
3	A	0.4	15	1.5	2.63
4	A	0.8	15	3	5.63
5	A	1.6	15	6	11.63
6	A	3.2	15	12	23.63
7	A	6.4	15	24	47.63
8	A	12	84	252.37	300
	Volume	Concentration (mcg/ml)		Total dose in each solution (mcg)	
Solution A	20 ml	15		300	

Discussion

Exogenous G-CSF delivery is based on recombinant DNA technology from bacteria or mammalian cells used to stimulate granulocyte production in neutropenic patients for various reasons or in bone marrow donors prior to the donation procedure. There are two humanized recombinant G-CSF drugs: Filgrastim derived from bacteria (*Escherichia coli*) and Lenograstim derived from mammalian cells (Chinese hamster ovary), but the latter is not authorized for administration in Europe. Subsequently, genetically modified microheterogeneous proteins have been developed, some of them with maintained function, such as Pegfilgrastim (pegylated form of Filgrastim) (4). G-CSF support is considered a safe treatment; however, Bumbacea analyzed up to 40 publications regarding hypersensitivity reactions to G-CSF, 18 of them immediate-onset. The sensitivity and specificity of skin prick and intradermal tests for Filgrastim and Pegfilgrastim are unknown, there are few publications that have conducted in vivo studies with these drugs (1,5,6,7,8). Some researchers have performed in vitro studies (antibodies and immunoglobulins) with variable results (5), but this is the first case described with the involvement of interleukins in a hypersensitivity reaction secondary to exogenous G-CSF administration. We decided to perform a desensitization protocol for Filgrastim, whose dosage and half-life are shorter than others like Pegfilgrastim, in order to avoid intense and persistent adverse reactions (9). Initially was used the 12-step regimen proposed by Jeter (3) and eventually developed an 8-step intravenous protocol that has been well tolerated to date (10).

In this case, G-CSF support is unavoidable, and the expectation is that it will be required for years. Therefore, monthly intravenous desensitization to Pegfilgrastim could be considered as a possible alternative to reduce frequency of hospital care assistance.

We concluded that:

- G-CSF supplements are considered safe treatments; however, some hypersensitivity reactions have been reported following their administration.
- The sensitivity and specificity of in vivo tests against Filgrastim and Pegfilgrastim are unknown, but in vitro tests can help us orient ourselves to the mechanism of their hypersensitivity reactions. In the case presented, a cytokine release reaction was demonstrated.
- Patients requiring exogenous administration of G-CSF have no therapeutic alternatives; however, we only found five publications in which desensitization protocols for these drugs were implemented.
- Finally, our patient was scheduled for a Filgrastim desensitization protocol, which allowed for its administration without incident.

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