

Letter to the Editor (Case report)

doi:10.1093/rheumatology/kez469

Polyethylene glycol: an underrecognized compound in certolizumab pegol and Movicol that may cause anaphylaxis**Rheumatology key message**

- PEG anaphylaxis is rare but potentially fatal, so checking of medication components before prescribing is essential.

SIR, We wish to report the case of a 37-year-old woman who was commenced on certolizumab pegol for PsA following failed trials with etanercept and ustekinumab in combination with methotrexate. In addition to PsA she had a history of allergic rhinitis and an anaphylactic reaction to Movicol for which she carried an adrenaline autoinjector pen. She attended an educational session at the rheumatology department regarding certolizumab administration. Upon returning home, she injected the first dose. Approximately 10 min later she noticed erythema around the injection site before developing a generalized urticarial rash, dyspnoea, wheeze and a sensation of presyncope. Her sister administered her adrenaline pen and she was transferred to her local emergency department.

On review in the emergency department, she was tachycardic at 112 beats/min, tachypnoeic at 25 beats/min and hypotensive at 112/49 mmHg but maintaining her oxygen saturation at 99% on room air. She received another dose of intramuscular adrenaline in addition to intravenous hydrocortisone, chlorphenamine and fluid resuscitation according to the anaphylaxis protocol. Apart from her vital signs, her physical examination was unremarkable. Sinus tachycardia was noted on her electrocardiogram and her chest X-ray was normal. The only abnormalities on her blood investigations were an elevated white cell count ($22.4 \times 10^9/l$), elevated lactate (7.1 mmol/l) and borderline CRP elevation at 8.7 mg/l. All other haematological investigations during the admission, including serum tryptase, were normal, however, this was checked >24 h after the initial exposure to certolizumab

pegol. Her previous baseline blood parameters had been within normal limits. She was admitted overnight for observation and remained stable.

On further questioning of her allergic history, she revealed that she had experienced an anaphylactic reaction to Movicol [polyethylene glycol (PEG) 3350] 2 years prior. This was the first occasion that she had taken this medication. Within minutes of ingestion, she recalled feeling dyspnoeic and wheezy with chest tightness before losing consciousness. When she came around, she had periorbital and tongue oedema with a generalized urticarial rash. She received urgent medical attention at her local emergency department and her symptoms resolved after several hours. Subsequently an adrenaline pen was prescribed for her and she was advised to avoid Movicol indefinitely.

Following liaison with the immunology and rheumatology departments in Galway University Hospitals, it was felt that the likely culprit for this patient's hypersensitivity reactions was the macrogol present in both Movicol and certolizumab. Her skin prick testing for allergens revealed a delayed equivocal reaction to Movicol [negative at 15 min but positive at 30 min with a 3×3 mm reaction at neat concentration (i.e. one sachet in 125 ml)]. Her adalimumab skin prick testing was negative at 1/100 (0.4 mg), 1/10 (4 mg) and neat concentrations (40 mg), thus confirming that the allergen was the PEG component rather than the anti-TNF portion of the drug (Table 1). Her serum tryptase was normal on repeated checking, ruling out mastocytosis.

Certolizumab pegol (Cimzia) is the only pegylated Fc-free anti-TNF monoclonal antibody currently available. Pegylation of biological proteins is when proteins and PEG undergo covalent conjugation. This confers increased drug stability due to properties such as longer half-life, increased solubility and a reduction in protein aggregation [1]. Macrogol is the international non-proprietary name for PEG. In pharmaceutical nomenclature, it is usually accompanied by a number that corresponds to its approximate molecular weight.

Macrogols are widely used in industry, including medications, cosmetics and detergents, for their stabilizing properties [2]. It is unclear whether the molecular weight

TABLE 1 Skin prick testing results

Test solution	1/100 dilution ^a	1/10 dilution ^a	Neat
Positive control	N/A	N/A	15 × 11 mm
Negative control	N/A	N/A	0 × 0 mm
Movicol (PEG 3350), 1 sachet/125 ml	1 × 1 mm at 15 min 3 × 3 mm at 30 min	1 × 1 mm at 15 min 3 × 3 mm at 30 min	1 × 1 mm at 15 min 3 × 3 mm at 30 min
Adalimumab 40 mg	0 × 0 mm	0 × 0 mm	0 × 0 mm

^aSolutions prepared with 0.9% normal saline, which does not contain macrogols.

of the macrogol or the route of administration can be implicated in the incidence of cross-allergies; this requires further investigation [1]. There have been several reports of macrogol-induced hypersensitivity reactions and anaphylaxis. The majority of reports describe reactions following ingestion of bowel preparations prior to colonoscopies, but there have been instances of anaphylaxis post-injection of a steroid solution, with antibiotics and sucking on a throat lozenge [2–6]. To the best of our knowledge, this is the first case report of macrogol anaphylaxis associated with certolizumab pegol.

The management of patients with macrogol allergies is challenging given that it is so widely used and may even be present in some medications used to treat reactions (e.g. antihistamines and steroids). Of note, macrogol is present in Depo-Medrone but not Solu-Medrone, both commonly used to treat flares of rheumatologic diseases. Our patient had previously received a Solu-Medrone injection without any adverse reaction. Methotrexate does not contain macrogol, which was continued in this setting. She was commenced on adalimumab in combination with methotrexate following skin prick testing and tolerated this well.

This case highlights the importance of inquiring about previous allergic reactions and yellow-card reporting of adverse drug reactions to manufactures. Patients with a documented anaphylactic reaction should be encouraged to carry an adrenaline pen on their person, regularly confirm that it is in date and wear a Medic-Alert bracelet.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 9 September 2019

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