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Case Report

D-dimer Increasing After First Alemtuzumab Administration in a Multiple Sclerosis Patient

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Abstract: Alemtuzumab is a humanized anti-CD52 monoclonal antibody used for the treatment of high activity relapsing multiple sclerosis (R-MS). The most common adverse event is an infusion reaction due to cytokine-release. Autoimmunity can arise from months to years after treatment and encompasses Grave's disease and thrombocytopenia. Recent reports of stroke, heart attack, and arterial dissection after alemtuzumab administration, in some cases within hours of infusion, led the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) to a safety review of treatment with alemtuzumab. We report a D-Dimer increasing with suspected associated pulmonary embolism in an RMS patient after the first alemtuzumab administration. D-dimer test is not mandatory after alemtuzumab treatment, but its possible increase should warn the physician to select the patients with lower cardiovascular and thrombosis risk.

Keywords: Multiple Sclerosis, Alemtuzumab, D-Dimer, Interleukin 6, Thrombosis, Biomarker, Manuscript

1. Introduction

Alemtuzumab is a humanized monoclonal antibody targeting the CD52 antigen, expressed mostly on T and B lymphocytes surface and in a less extent on natural killer (NK) cells, monocytes, and dendritic cells [1], approved for the treatment of relapsing multiple sclerosis (R-MS). A few minutes after infusion of a single alemtuzumab dose, peripheral lymphocytes are depleted, probably as a consequence of antibody-dependent, cell-mediated cytotoxicity [2]. Cross-linking of NK cells determines the increase of serum cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interferon (IFN)-γ [3], with consequent infusion-associated reaction (IAR). Pre-treatment with high dose corticosteroids for the first 3 days and antihistamine drugs is prescribed to reduce IAR symptoms, such as fever and cutaneous rush [4]. Other side effects encompass infections and autoimmunity reactions, mainly versus thyroid (Graves Basedow disease), kidney (Goodpasture syndrome) and platelets (autoimmune thrombocytopenia), which can occur months or even years after alemtuzumab treatment [1]. IAR-related cardiac alterations such as tachycardia, bradycardia and palpitations are rare [1]. Recently, reports of stroke, heart attack, and arterial dissection after alemtuzumab administration, in some cases within few hours after infusion, led the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) to restrict the use of alemtuzumab to adults with highly active R-MS, despite treatment with at least two disease-modifying therapies or where other disease-modifying therapies cannot be used [5].

As of March 18, 2019 D-dimer increased is reported only by 3 patients treated with alemtuzumab among 4.420 people who have side effects while taking alemtuzumab (FDA report) [6]. All patients were middle-aged and treated with alemtuzumab for T-cell depletion and multiple myeloma [6].

Corticosteroids, used in alemtuzumab pre-treatment, are well known as causing significant cardiovascular side effects [7].

2. Case Report

A 24-year-old woman with highly active R-MS was started on alemtuzumab 12 mg 1 vial intravenously, after trying natalizumab, interrupted after the second administration following an allergic reaction, and mitoxantrone (total dose reached 120 mg). Among the co-pathologies, we report obesity (Body Mass Index 43) and sporadic migraine, not under prophylactic treatment. The patient does not smoke and does not take the contraceptive pill. All blood and urinary tests performed before alemtuzumab were normal except for fibrinogen and reactive C protein (CRP) that were slightly beyond standard limits. After corticosteroid pre-treatment and during the first alemtuzumab administration, the patient complained about severe headaches, different from the usual one experienced. Considering the headache features, the pre-treatment with steroids and the cardiovascular risk associated with obesity, D-dimer was dosed. D-dimer resulted highly increased (38000 ng/dL). Vital signs revealed blood pressure 125/70 mmHg, heart rate of 80 beats per minute, body temperature of 37.1°C and oxygen saturation was 97%. To exclude cerebral venous thrombosis patient underwent brain angio-CT scan, which resulted normal. There were no signs of peripheral thrombosis. Arterial blood gas test showed mild hypocapnia (28.3 mmHg) and mild hyperoxia (147 mmHg). Pulmonary perfusion scintigraphy revealed reduced tracer uptake in the *lingula*. this finding was compatible with pulmonary thromboembolism. The patient received enoxaparin 10000 I. U. subcutaneously. The day after the patient underwent a pulmonary angio-CT scan, with no signs of thromboembolism, and D-dimer control, which showed a reduction (15452 ng/mL). No further doses of alemtuzumab were administered. One month before alemtuzumab treatment, following the patient's written consent, we collected serum in order to analyze the further change in lymphocytes subset, as the patient participated in an immunological study. After this adverse event occurred, we used the patient's serum to detect TNF-α, IL-6 and IFN-γ levels. We thus measured that cytokines levels also the day of alemtuzumab administration. An increase of IL-6 was observed at the time of administration (106±11,6 pg/ml) compared to pre-treatment (65±3,1 pg/ml).

3. Discussion

Alemtuzumab is an immunosuppressive drug that rapidly reduces B and T lymphocytes and is associated with an increase of serum proinflammatory cytokines, as IL-6 [3], a biomarker of inflammation [8]. IL-6, a circulating cytokine produced by monocytes, macrophages, T lymphocytes and endothelial cells, plays a central role in the hepatic production of CRP, fibrinogen, and other acute-phase proteins involved in the inflammatory process [9] and can promote a prothrombotic state by increasing expression of fibrinogen, tissue factor, factor VIII and von Willebrand factor, as well as by activating endothelial cells and increasing platelet production [9]. D-dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis; it is not usually present in human blood plasma, except when the coagulation system has been activated, for instance, because of the presence of thrombosis or disseminated intravascular coagulation. D-dimer is also an acute-phase reactant whose production stimulates high levels of cytokines such as IL-6 that, in turn, may promote neutrophil and monocyte activation, inducing the further release of IL-6 [10].

Human Immunodeficiency Virus (HIV)-positivity in the adult population, a condition characterized by low CD4+lymphocytes similarly to alemtuzumab treatment, higher levels of IL-6 and D-dimer are associated with an increased risk of cardiovascular disease [11].

Our patient had also two other cardiovascular risk factors: pre-treatment with corticosteroids and severe obesity. Of note, an increase of IL-6 was associated with a higher BMI and suggested as a marker of inflammation, and endothelial dysfunction state in obesity [12].

4. Conclusion

D-dimer test is not necessary during or after alemtuzumab therapy, although, its possible increase in a prothrombotic status following inflammation as a consequence of proinflammatory cytokine release, including IL6, makes it a useful biomarker in patients at greater thrombotic risk.

In an HIV setting, a recent study [13] developed a biomarker score (the "IL-6 & D-dimer score"), which combines markers of inflammation and coagulation to predict the cardiovascular risk among HIV-infected adults. Such a score could be an appropriate biomarker to identify possible high cardiovascular risk in MS patients before and after first alemtuzumab dose, in order to tailor the MS-therapy with alemtuzumab, reducing the vascular risk, also considering the emerging reports of thrombotic acute episodes during or after alemtuzumab treatment [5].

Author Contributions

Stefania Federica De Mercanti and Simona Rolla share co-first authorship

SFDM clinical evaluation and paper writing
SR biological analysis and paper writing
MM clinical evaluation and paper writing
MI clinical evaluation and paper writing
EF clinical evaluation and paper writing
MC clinical supervision, paper revision

Conflict of Interest Statement

SFDM received travel grants from Sanofi-Genzyme
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MM received travel grants from Biogen and Novartis
MI has nothing to disclose

EF has nothing to disclose

MC received personal compensations for advisory boards, public speaking, editorial commitments or travel grants from Biogen Idec, Merck Serono, Fondazione Serono, Novartis, Pomona, Sanofi-Genzyme and Teva.

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