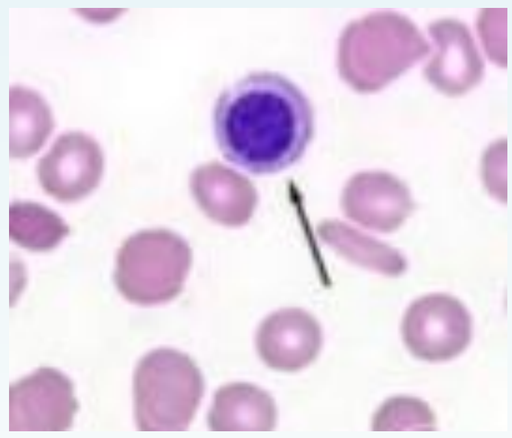
Regression of erythroblastaemia in natalizumab-treated patients with multiple sclerosis after drug suspension.

Sara La Gioia, V. Barcella, M. Conti, B. Frigeni, C. Zanchi, M. Vedovello, M. Rottoli
ASST Papa Giovanni XXIII - USC Neurologia – USS Malattie Autoimmuni – Centro Sclerosi Multipla Bergamo - Italy

INTRODUCTION AND OBJECTIVES:
Natalizumab is a monoclonal antibody that significantly reduces the occurrence of relapses in relapse-remitting multiple sclerosis (RRMS) patients. It is a recombinant antibody directed against the lymphocyte α4 subunitofthe α4 β1 (VLA-4) integrin. It prevents the binding betweenVLA-4 and vascular endothelium cell adhesion molecule1(VCAM-1), which, overtime, decreases α4 expression, resulting in a reduced extravasation of inflammatory immune cells across the blood-brain barrier into the central nervous system. Due to modifications of the bone marrow vascular niche and the interference of natalizumab with the homing of haematopoietic stem cells, the major haematologic finding in patients treated with natalizumab relates to the number of CD34 +cells, which rapidly egress from the bone marrow cavity into the peripheral blood. VLA-4 also play a critical role in erythropoiesis, being essential for the terminal proliferation and differentiation of erythroid progenitor cells. Erythroid cells specifically express fibronectin receptors α4 β1,and the engagementof α4 β1 integrin by fibronectin provides signals that are necessary for the terminal expansion of differentiating erythroblasts. Erythroblastaemia has been previously reported as a frequent finding of natalizumab treatment in multiple sclerosis patients. Its long-term clinical or pathological implications are still to be understood.
We investigated the persistence of erythroblastaemia after natalizumab suspension.

MATERIALS AND METHODS:
We retrospectively evaluated the blood samples of 15 subjects with confirmed erythroblastaemia during natalizumab and who were withdrawn from treatment.
Peripheral whole blood samples were collected in K3 EDTA blood tubes (Becton Dickinson,FranklinLakes,NJ), processed on XN-9000 (SysmexCo.,Kobe,Japan) and analyzed. The cell blood count (CBC) and extended leukocytedifferential count was always performed within 2 hours from sample collection (blood draw). XN-9000analyzer has aspecific channel (WNR) for erythroblasts/nucleated red blood cells NRBCs counting based on optical fluorescence system associated with a specific lysing agent which is responsible for selective red blood cells (RBCs)lysis. The blood smears were automatically prepared with Autoslider SP- 10 slidemaker (SysmexCo.,Kobe,Japan) and then stained with May-Grünwald-Giemsa (Carlo Erba Reagents S.p.A. Milano,Italy). The blood smear review process was performed with DI60 SysmexCo.,Kobe,Japan). Both Autoslider SP-10 and DI60 were physically connected with the XN-9000 analyzer. The digital images were then reevaluated and validated by a skilled specialist in laboratory hematology, according to the CLSI standard H20-A2 and ICSH guideline. Samples were confirmed positive on microscopic review when NRBCs were >= 1/200 white blood cells (WBCs) (or >=0.5%) in accordance with the criteria described in Standard International Consensus Group for Hematology.

RESULTS:
Our sample consisted of 15 patients, 5 males and 10 females, with a mean oge of 31.5 years (median 31). All our patients had been treated with more than 12 natalizumab infusions (mean 42.27 infusions, median 40, range 19-97) and they all discontinued treatment due to evidence of positivity for antiJCV antibodies. Erythroblastaemia was present in all cases at the last blood sample before the last drug administration (NRBCs median 0.020, IQR 0.010-0-030, 10 *9/L). Erythroblasts were absent (NRBCs median 0.000, IQR 0.000-0.000, 10 *9/L) in all blood samples of our patients after a mean time of 2.8 months (range 1-4 months) after drug
suspension.



DISCUSSION AND CONCLUSION
The prevalence of erythroblastaemia has been previously reported to be significantly higher in patients treated with natalizumab compared to patients on other multiple sclerosis treatments. These previous data raised some issues on long term pathological implications. Our last findings support the hypothesis of erythroblastaemia as a transient phenomenon during natalizumab treatment: it appears then acceptable to refrain from further diagnostic procedures during treatment in the absence of any other laboratory results suggesting underlying disorders. A larger sample of patients is needed to confirm our data.

References:
- La Gioia S, Seghezzi M, Barcella V, Dominoni P, Mecca T, Frigeni B, Conti MZ, Vedovello M, Vidali M, Rottoli M, Buoro S. Erythroblastaemia in natalizumab-treated patients with multiple sclerosis. Mult Scler Relat Disord. 2016 Jul;8:141-4.
- Robier C, Amouzadeh-Ghadikolai O, Bregant C, Diez J, Melinz K, Neubauer M, Quasthoff S. The anti-VLA-4 antibody natalizumab induces erythroblastaemia in the majority of the treated patients with multiple sclerosis. Mult Scler. 2014 Aug;20(9):1269-72.

Sistema Socio Sanitario
Ospedale di Bergamo
Regione Lombardia
ASST Papa Giovanni XXIII