Circulating endothelial progenitor cells in ANCA-associated vasculitis: the light at the end of the tunnel?

The main clinical features of ANCA-associated vasculitis (AAV) are inflammation and necrosis of small vessels, thrombus formation and endothelial injury [1–3]. In this issue of Rheumatology, Závada et al. [4] conclude that low numbers of circulating endothelial progenitor cells (EPCs) are associated with increased propensity for early relapse of AAV.

The therapeutic potential of EPCs in AAV may exist in the form of four different scenarios. First, although disease remission is achieved by most patients, morbidity (pulmonary fibrosis, chronic renal failure and neuropathy) is present in ~90% of the patients with AAV [3]. Consequently, it is important to decrease morbidity in this disease. This decrease may be possible by increasing EPC levels, considering that EPC augmentation (by drugs—statins, GM-CSF or VEGF—or by transplantation) has been associated with good outcomes in other diseases with vascular inflammation/endothelial injury, such as ischaemic stroke (good functional outcome and reduced infarct growth), acute myocardial infarction (improved global left ventricular ejection fraction, reduced end-systolic left ventricular volume reduction, increased coronary blood-flow reserve and improved myocardial viability), coronary artery disease and atherosclerosis [3, 5, 6].

Although GM-CSF may mobilize stem cells to re-endothelize damaged vessels, it cannot be used in AAV patients, considering that the resulting neutrophilia may trigger a relapse [3].

Secondly, at present, thrombosis in AAV represents a novel clinical conundrum. The incidence of thromboembolic events in WG/AAV is as high as in patients with previous idiopathic venous thromboembolism (7.0 cases/100 patient-years vs 7.2 cases/100 patient-years, respectively) [2, 7, 8]. Considering that the prophy­lactic use of statins is an effective method to prevent thromboembolic events in healthy men and women with low-density lipoprotein (LDL) cholesterol levels <3.4 mmol/l and high-sensitivity CRP levels of ≥19.05 mmol/l, it is possible that prophylactic statins may also benefit AAV patients [9]. Prophylactic use of statins may be especially important during disease activity, because 81% of thromboembolic events take place in individuals with active vasculitis. The possible benefits of statins in thrombo­sis are mediated by increasing EPC levels, reducing vascular inflammation (anti-inflammatory effect), decreasing platelet aggregation and inhibiting thrombus formation [8, 9]. However, the possible benefits of statins in AAV patients would need to be addressed by a randomized controlled trial.

Thirdly, other important scenarios in AAV are treatment resistance and disease relapse. At 6 months, the remission rate in patients treated with cyclophosphamide is ~90%, and relapse rates at 18 months are 40–50% [1, 4, 7]. Considering that EPC participates in the repair of damaged endothelium and can prevent endothelial activation, low EPC levels may predispose to early AAV relapse [4]. In addition, the increase in EPC levels (by transfusion or drug administration, such as statins) may diminish the rates of treatment resistance and disease relapse, and may still shorten the duration of treatment with immunosuppressants, which are associated with cancer, haemorrhagic cystitis, pulmon­ary fibrosis and infection [1, 4].

Finally, AAV is still associated with accelerated atherosclerosis. Sangle et al. [10] showed that patients with systemic vasculitis have an increased prevalence of abnormal ankle-brachial pressure index, denoting a high risk of cardiovascular disease. Consequently, the increase in EPC levels in AAV (by transfusion or drug administration) could also improve the cardiovascular outcome, as observed in acute myocardial infarction and ischaemic stroke [5, 6].

The study by Závada et al. [4] has some drawbacks. First, there is continuing debate about the perfect method for EPC assessment (early endothelial outgrowth cultivation method or flow cytometric approaches), and the EPC assessment may influence the results obtained. Therefore, it is important to repeat this study with flow cytometric approaches.

Secondly, among the 41 patients enrolled for the initial EPC sampling, 31 patients had active disease and 10 were in remission. Furthermore, only 10 patients were sampled twice during the course of the disease. Nevertheless, the ideal design of this study would have been to enrol 41 patients with active disease for the initial EPC sampling and to have all the 41 patients sampled again after disease remission.

Thirdly, there was no significant difference in EPC numbers between the subgroups of AAV patients with and without active disease, while this difference was verified in another study, corroborating the need for more studies in this field of research [4].

Fourthly, the limited number of patients of the referred study did not allow a robust multivariable regression analysis, precluding any definitive assumptions [4]. Regardless of some divergent results regarding EPCs in AAV, it seems clear that EPCs have some role in this disease [3, 4].

Considering all these data, the increase in EPC levels in AAV may represent the light at the end of the tunnel. EPC increase may solve the problems of chronic morbidity, thromboembolic events, treatment resistance, disease relapses, secondary malignancy, opportunistic infection and accelerated atherosclerosis in AAV. However, this use needs to be addressed by a randomized controlled trial.

Acknowledgements

The author would like to thank Prof. C. R. R. Carvalho and Prof. R. Souza for their comments in the preparation of this manuscript.

Disclosure statement: The author has declared no conflicts of interest.

Alfredo N. C. Santana

1Hospital Regional Publico Araguaia/IDESMA and University of Sao Paulo, Sao Paulo, Brazil

Accepted 22 June 2009

Correspondence to: Alfredo N. C. Santana, Ru­a Maraba 21, CEP 68550-490, Redencao, PA, Brazil.

E-mail: alfredonicodemos@hotmail.com

References

6 Sobrino T, Hurtado O, Moro MA et al. The increase of circulating endothelial progenitor cells after acute ischemic stroke is associated with good outcome. Stroke 2007;38:2759–64.