Revista Electrónica de Biomedicina
Electronic Journal of Biomedicine

ISSN: 1697-090X

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Rev Electron Biomed / Electron J Biomed 2015;2:8-12.

Editorial:

A NEW HORIZON IN THE IMMUNOSUPPRESSIVE TREATMENT OF ACQUIRED APLASTIC ANEMIA

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Version en español

Aplastic anemia (AA) is an acquired bone marrow disease characterized by the absence of hematopoietic progenitor due to an immune attack [1].

It has an incidence of 1-4 cases per million per year, affects both sexes equally, and has 2 clearly defined peaks when it appears: in the young and in people over 60 years old.

The standard immunosuppressive treatment of AA has been the combination of horse or rabbit antithymocyte globulin and cyclosporine, with a response being achieved in 60% of cases.

It has been postulated that the patients that were treated with horse antithymocyte globulin (hATG) had a better hematological response

and overall survival than those who received rabbit antithymocyte globulin (rATG)[2].

However, the Spanish Group for the Study of Aplastic Anemia showed that there were no significant differences between the two globulins. The response at three months was 63% in the group that received rATG compared to 66 % in the hATG group. It was also observed that at 12 months there was a change in the response in 84% of the patients that received rATG compared to 76 % of those that received hATG, and was, therefore, concluded that they are equivalent[3].

Up until now, there was no effective treatment for patients with refractory or recurrent disease and without a compatible donor and in those that are not candidates to transplant, and a palliative treatment was established with hemotherapy and antibiotics for the treatment of infection complications.

Thrombopoietin is the principle regulator of platelet production and acts by binding to the megakaryocyte receptor, c-MPL, which triggers their maturity and subsequent production of platelets.

Eltrombopag is an oral thrombopoietin-mimetic drug that binds to this receptor and promotes megakaryopoiesis and platelet formation[4].

It is a drug that has demonstrated its efficacy in patients with AA, given that the stem and hematopoietic progenitor cells also express c-MPL receptor on their surface. Thus, it is assumed that eltrombopag could act by stimulating overall hematopoiesis[5].

Olnes et al[6] treated 25 patients with this drug with doses from 50 mg up to a maximum of 150 mg for 12 weeks and achieved a hematological response of at least one hematopoietic line in 44 % of the patients. This study had the particular characteristic in that it performed serial bone biopsies, noting that the 3 hematopoietic lines were returning to normal (when a response was seen), with no increase in bone marrow fibrosis.

One concern in these patients is the possible clonal evolution after taking the drug. In this study, a monosomy 7 was observed in 2 patients without a response, but did not produce a clonal evolution in patients that had shown a response.

It should be pointed out that, in the observation of historic series, 10-15% patients with AA present with clonal evolution[6].

As regards clonal evolution, the authors hypothesized that eltrombopag could stimulate the expansion of latent clones that,

perhaps, were initially below the limit of detection of the metaphases. However, a study using comparative genomic hybridization (CGH-SNP arrays) was performed on the patient specimens, and no evidence was found of pre-existing clones.

Another hypothesis suggests that the chronic pharmacological stimulation could have led to the hematopoietic progenitor proliferation and the presence of shortened telomeres or other disturbance due to the deficit of stem cells or by a chronic immune attack, giving rise to the subsequent destabilization of the genome, accelerating the emergence of abnormal genes[7].

An extension study has subsequently been published, in which it increases the number of patients and proposes to stop eltrombopag if a response is obtained: the patients must achieve these figures: > 50 x 10 9 platelets, > 10 gr/dl of hemoglobin, > 1 x 10 9 neutrophils); 17 (40%) out of the 43 patients in this group responded.

Finally, 5 patients met the criteria to stop the drug and remained stable during 13 months follow-up. There were subsequently 3 relapses and eltrombopag was re-started at a dose of 150 mg, and only one of them achieve a response in red cells. Clonal evolution occurred in the sub-group of refractory patients [7].

Given that standard immunosuppressive treatment requires the use of cyclosporine, a study was conducted on healthy volunteers to investigate the pharmacokinetic effect of taking the combination of cyclosporine and eltrombopag, with it being demonstrated that it is not required to adjust the cyclosporine dose when both drugs are administered together [8].

Due to the expectation generated by the use of eltrombopag in AA, Townsley et al, proposed a study in which eltrombopag is combined with standard immunosuppressive treatment.

They evaluated 88 patients treated with horse antithymocyte globulin together with cyclosporine and eltrombopag. This was administered at a dose 150 mg in 3 different cohorts: in the first and second it was introduced from day 14 (after the immunosuppressive treatment was administered) up to 6 months and up to 3 months. In the third cohort, eltrombopag was administered from the start of the immunosuppressive treatment, that is, given concomitantly.

The analysis of the response at 6 months produced surprising results in the third cohort, with 92% of complete responses. With a follow-up of 15 months, cytogenetic changes were observed in 7 patients, detecting that the clonal evolution to myelodysplastic syndrome has a similar frequency to that of the historic group that received standard immunosuppression [9].

In view of these results, there should be a change in the standard treatment of acquired aplastic anemia in the future, to immunosuppressive treatment and a new drug should be added to cyclosporine since eltrombopag has demonstrated that it is effective and safe, since the number of clonal events does not increase after its use.

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