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ORIGINAL ARTICLE

Androgens added to immunosuppressive regimen in patients with aplastic anaemia. A retrospective study

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KEYWORDS
Aplastic anaemia;
Androgens;
Treatment outcome;
Immunosupression;
Cohort study

Abstract
Background: Androgens have been used to treat bone marrow failure syndromes such as aplastic anaemia (AA) since the 1970s, and are currently used as adjuvants to other treatment regimens.
Objective: To determine the efficacy and response time of androgens in the treatment of AA.
Materials and methods: A retrospective, analytical-observational nested study in a cohort of patients with AA. The study was conducted from January 2006 to December 2013.
Results: A total of 63 patients with a mean age of 47 (18–83) years were included in the study. Out of 27 patients in full remission, 17 received some type of immunosuppressant combined with androgens. The use of more than 2 immunosuppressants did not significantly improve response times ($p = 0.311$, 95% CI). Mean response time was 725 (331–1119) days; 4-year survival rate was 86%.
Conclusions: Improved immunosuppressant response rates with adjuvant androgens were mainly observed in patients with severe AA.

PALABRAS CLAVE
Anemia aplásica;
Andrógenos;
Resultado del tratamiento;
Inmunosupresión;
Estudio de cohorte

Cohorte retrospectiva de la adición de andrógenos al régimen inmunosupresor en pacientes con anemia aplásica

Resumen
Antecedentes: Desde los sesenta se utilizan andrógenos para tratar síndromes de falla medular, como la anemia aplásica (AA), actualmente son complemento a otros tratamientos.
Objetivo: Establecer la eficacia y tiempo de respuesta al tratamiento con andrógenos en AA.
Material y Métodos: Estudio retrospectivo, observacional-analítico anidado en la cohorte de pacientes portadores de AA durante enero 2006 a diciembre 2013.

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Resultados: Se estudiaron 63 pacientes, con edad media de 47 (18–83) años. De 27 pacientes (42.9%) que integraron remisión completa, 17 recibían algún inmunosupresor en conjunto con andrógenos. Usar más de 2 inmunosupresores elevó no significativamente ($p = 0.311$, 95%IC) las respuestas. La media de respuesta fue de 725 (331–1,119) días. La supervivencia a 4 años fue del 86%.

Conclusiones: Adicionar andrógenos mejoró la tasa de respuesta a los inmunosupresores principalmente en pacientes con AA muy severa.

Introduction

Aplastic anaemia (AA) is an immune disease characterized by varying degrees of peripheral cytopaenia and fatty replacement of haematopoietic tissue.[1] Response to immunosuppressants varies, but cyclosporine plus antithymocyte globulin (ATG) generally achieves a response rate of over 60%.[2,3] The combination of haematopoietic stem cell transplant and immunosuppressant therapy has increased the survival rate of AA patient to over 80% worldwide, with a second cycle of ATGs or administration of new thrombomimetic drugs being reserved for refractory cases.[4,5] Prior to these therapeutic advances, evidence from a number of case series led to androgens being included in regimens to treat bone marrow failure syndromes.[6,7] In the 1970s, attempts were made to combine them with other options such as steroids,[8,9] but it was not until the end of that decade that they were first combined with haematopoietic stem cell transplant.[9,10] In the mid 1980s, Champlin et al. published the first prospective study in 121 patients receiving androgens as adjuvant to ATGs. The study found no significant differences in remission rates.[11] Following this, interest in androgens faded, and their use was limited to a few small series. In Mexico, Pérez et al. evaluated the efficacy of danazol as first line therapy, and reported a mean response time of 3 months, with an overall response rate of 46%.[12] In the General Hospital of Mexico, standard treatment is based on immunosuppressants in combination with different types of androgens. The main aim of this study has been to evaluate combination therapy with androgens and immunosuppressants in terms of response time and rate.

Methods

Study design

We carried out a retrospective chart review of patients with acquired AA seen in the General Hospital of Mexico from January 2006 to December 2013.

All patients meeting diagnostic criteria for AA whose primary treatment had included androgens alone or in combination with immunosuppressants. Diagnosis of AA was defined by at least 2 of the following criteria: haemoglobin less than 10 g/dL, platelet count less than 50×10^9/L, neutrophil count less than 1.5×10^9/L and hypercellular bone marrow.

Exclusion criteria were: incomplete medical record, therapy including bone marrow stimulants, evidence of paroxysmal nocturnal haemoglobinuria (PNH) with haemolysis, history of thrombosis associated with PNH or clone greater that 50% on flow cytometry, pregnancy, or prior diagnosis of malignancy.

The clinical and laboratory reports of study patients at the time of diagnosis, together with the therapy used, the clinical course, transfusion requirements, and date of the last visit were recorded. Cases were categorized as moderate and severe AA according to severity, which was assessed on the basis of neutrophil and platelet count at the time of diagnosis. The severe group was later divided into severe and very severe.[13]

Treatment protocol

The immunosuppressant cyclosporin A (CpA) was administered daily (5 mg/kg) to maintain levels of 150–250 ng/mL. Other immunosuppressants used in combination with CpA were mycophenolate mofetil and prednisone (1 mg/kg). Red blood cell (RBC) or platelet transfusion was ordered at the discretion of the attending physician. Response to treatment was evaluated on the basis of established criteria.[13]

Androgens

The androgens most commonly used were danazol and mesterolone, followed by testosterone and oxymetholone. Danazol was given orally at 200 mg every 8 h, and was either stepped down or suspended at the discretion of the attending physician.

Ethical considerations

Being a retrospective study, the data were sourced from medical records held in the Haematology Departments. Access to these was strictly controlled, in accordance with regulations in force in Mexico, and patient privacy and anonymity was maintained at all times.

Statistical analysis

Study data were analyzed using IBM SPSS version 20.0 (Armonk, New York). Overall survival was estimated using Kaplan–Meier curves; response of each severity category