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**Is Horse Antithymocyte Globulin (ATG) plus Cyclosporine (CsA) the most effective first-line therapy for patients with bone marrow failure disorders?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

**OBJECTIVE:** The objective of this selective Evidence Based Medicine review is to determine whether or not Horse Antithymocyte Globulin (ATG) plus Cyclosporine (CsA) is the most effective first-line therapy for patients with bone marrow failure disorders.

**STUDY DESIGN:** Review of two randomized control trials (RCTs) and one single-center retrospective study, which were published between 2010 and 2013. All studies were published in the English language.

**DATA SOURCES:** Two randomized control trials and one single-center retrospective study published in peer-reviewed journals, which were found using PubMed.

**OUTCOMES MEASURED:** Each of the three trials measured the patient-oriented outcome of overall survival. Shin et al also assessed failure free survival. Survival was measured at different year markers after therapy between all three studies and also implemented the use of the Kaplan Meier curve for overall survival.

**RESULTS:** Scheinberg et al (2011) was the only study which yielded statistically significant data supporting Horse ATG plus CsA as the superior therapy for patients with bone marrow failure disorders (p-value = 0.04). Both the Passweg et al (2010) and Shin et al (2013) studies demonstrated inconclusive data, as the results in each study did not yield a statistically significant difference between the three treatment modalities: Horse ATG plus CsA, Rabbit ATG plus CsA, or Basic Supportive Care (BSC).

**CONCLUSIONS:** Results were inconclusive due to only one of the three studies demonstrating data to support Horse Antithymocyte Globulin as the best initial treatment for patients with bone marrow failure disorders.

**KEY WORDS:** Aplastic Anemia, Myelodysplastic Syndrome, Anti-Thymocyte Globulin, Cyclosporine

## INTRODUCTION

Bone marrow failure disorders are acquired or inherited rare diseases in which one or all cell lines of the bone marrow are affected: it fails to produce a sufficient supply of red blood cells, white blood cells, and/or platelets.<sup>1</sup> It is estimated that Aplastic Anemia affects 4 out of 1 million people in the United States per year, whereas Myelodysplastic syndromes affect more than 15,000 people in the United States per year.<sup>1</sup> There is no readily available data which describes the annual healthcare costs nor annual healthcare visits for patients with these conditions. However, a variety of factors influence these costs and healthcare visits because of the very unique patient population. Factors that influence the number of healthcare visits include out-patient clinic visits/follow-up appointments, emergency room visits, spontaneous hospital admissions, and a patient's comorbid conditions.<sup>2</sup> With that being said, it is also difficult to delineate an average price for the amount of care that goes into these patients. However, the following studies in this selective Evidence Based Medicine review demonstrate one treatment route in which costs are completely covered: clinical trials.

Although most cases of Aplastic Anemia and MDS are idiopathic, there are some theories as to what may trigger or cause these conditions: chemotherapy, radiation therapy, benzene or other toxic chemicals, and certain viral infections.<sup>1</sup> Diagnosing these conditions is difficult because the symptom presentation is so broad and may resemble other more benign illnesses. Common symptomatology is due to a deficit in one or more of the blood cell lines. Red blood cells (RBCs) are responsible for transporting oxygen throughout the body. A deficiency in RBCs would produce symptoms including fatigue, weakness, pallor, and dyspnea. A deficiency in platelets, which are responsible for clotting blood, may produce symptoms such as unexplained bleeding/bruising and petechiae. White blood cells play a significant role with helping the body

fight infection and foreign invaders; therefore, a deficit in these cells could cause fevers and/or frequent infections.<sup>1,3</sup>

Treatment for both Aplastic Anemia and MDS depends on a variety of factors including age of the patient, the patient's general well-being, and the severity of the patient's disease. One option for patients with more mild forms of their disease is supportive care. The purpose of supportive care is to help with the management of symptomatology to help with improvement in quality of life; this includes blood transfusions and growth factor therapy. Immunosuppressive therapy is another treatment modality which is reserved for patients with moderate to severe disease who necessitate medicinal intervention. This includes polyclonal antibody therapy such as Antithymocyte Globulin or oral immunosuppressants such as Cyclosporine or Mycophenolate Mofetil. Chemotherapy and radiation is also an option, which can help with the destruction or complete cessation of division of immature/defective blood cells. Finally, the gold standard treatment for any bone marrow failure disorder is blood and bone marrow stem cell transplantation to replace the damaged blood cell lines in the bone marrow.<sup>1</sup> However, many patients do not qualify for this treatment modality due to not having an adequately matched donor or having their condition be too poor to tolerate the long process of a transplant.

Currently, there is no known or proven immunosuppressive cure for bone marrow failure disorders, especially for those who cannot feasibly receive transportation, which is the only known cure for these diseases;<sup>4</sup> however the aforementioned treatment methods have helped to improve symptoms, quality of life, and have prolonged the lifespan in patients who suffer from these diseases.<sup>1</sup> Horse ATG is being evaluated as a reliable first line therapy for patients with bone marrow failure disorders who do not have matched bone marrow or stem cell donors.

## OBJECTIVE

The objective of this selective Evidence Based Medicine review is to determine whether or not Horse Antithymocyte Globulin (ATG) plus Cyclosporine (CsA) is the most effective first-line therapy for patients with bone marrow failure disorders.

## METHODS

The criteria for this selective Evidence Based Medicine review evaluates two randomized control trials and one single-center retrospective study, which were chosen based on population, intervention, comparison groups, and outcomes measured. The selected population of interest was patients with bone marrow failure disorders, specifically Aplastic Anemia and Myelodysplastic Syndrome. The intervention in these three studies was Horse Antithymocyte Globulin combined with Cyclosporine. The treatment group whom received the aforementioned intervention was compared to the experimental group who, based on the study, either received Rabbit Antithymocyte Globulin with Cyclosporine or Basic Supportive Care. The outcomes measured in each of these three studies was overall survival. One study also measured the outcome of failure free survival.

The following keywords were entered and searched on PubMed to uncover articles relevant to the clinical question that also included results consistent with patient oriented outcomes. All articles were published in English between 2010 and 2013 in peer reviewed journals. The inclusion criteria was as follows: at least two randomized control trials containing patients with a diagnosis of either Aplastic Anemia or MDS published during or after the year 2010. The exclusion criteria were any of the aforementioned patients who had received prior immunosuppressive therapies or who had severe comorbid conditions. The statistics used and

reported in this study were p-values, numbers needed to treat (NNT), and confidence intervals (CI).

Table 1 – Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Scheinberg <sup>4</sup> (2011)	RCT	120	2-77 years of age	-Aplastic Anemia with bone marrow cellularity <30%, plus two of the following: absolute neutrophil count less than 500, platelet count less than 20,000, absolute reticulocyte count less than 60,000 -Age > 2 years -Weight > 12 kg	-Fanconi’s anemia diagnosis, evidence of clonal disorder or cytogenetics, prior immunosuppressive therapy, infection, HIV, severe comorbid conditions, cancer patients currently undergoing chemotherapy, pregnancy, language barrier	Not noted	Horse ATG 40 mg/kg of body weight/day x 4 days plus Cyclosporine 10 mg/kg/day x 6 months
Passweg <sup>5</sup> (2010)	RCT	88	> 18 years	-MDS diagnosis, - Refractory anemia with or without sideroblasts or with excess blasts -Transfusion dependence for less than 24 months -Age > 18 years -Eastern Cooperative Oncology Group performance status > 2	-Patients with chronic myelomonocytic leukemia, refractory anemia with excessive blasts in transformation, secondary MDS, or infection	5	Horse ATG 15 mg/kg x 5 days and oral Cyclosporine (CsA) x 180 days

Shin <sup>6</sup> (2013)	Single center retrospective study	99	> 15 years	-Adults with Severe Aplastic Anemia who received first-line therapy with horse ATG or rabbit ATG at Seoul St. Mary's Hospital between February 2001 and May 2010	-Prior immunosuppressive therapy, bone marrow findings consistent with MDS, or <15 years of age	Not noted	Horse ATG 15 mg/kg/day x 5 days plus Cyclosporine 5-6 mg/kg/day x as long as patient was responding nor developing renal complications
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OUTCOMES MEASURED

The outcomes in this selective Evidence-Based Medicine review are reported as patient-oriented outcomes. The outcomes include overall survival, which was measured at different year markings post ATG therapy depending on the study, and failure free survival measured 5 years after ATG treatment.

The Scheinberg et al randomized control trial measured overall survival at 3 years in Aplastic Anemia patients who received Horse ATG with CsA compared with overall survival at 3 years in those Aplastic Anemia patients who had received Rabbit ATG with CsA. Overall survival at 3 years was determined using the Kaplan Meier curve which recorded the patients' hematologic response at 6 months after treatment in both groups.<sup>4</sup>

The Passweg et al randomized control trial measured overall survival at 2 years in low to intermediate risk myelodysplastic patients who received Horse ATG and CsA compared to the overall survival at 2 years of low to intermediate risk MDS patients who received basic supportive care.<sup>5</sup>

The Shin et al single center retrospective study measured overall survival and failure free survival at 5 years in Severe Aplastic Anemia patients who received Horse ATG with CsA compared to the survival of those who received Rabbit ATG plus CsA. The Kaplan Meier curve

was for overall survival was used to determine the survival data by assessing complete hematologic response at 3, 6, 12, and 18 months after ATG therapy in both groups.<sup>6</sup>

## RESULTS

This selective evidence-based medicine review evaluates Horse Antithymocyte Globulin (ATG) with Cyclosporine as a first line treatment for patients with bone marrow failure disorders. The results of these studies were presented in dichotomous data. Two of these studies were randomized control trials while one was a single-center retrospective study.<sup>4,5,6</sup>

Scheinberg et al<sup>4</sup> is a randomized control trial which assessed the efficacy of Horse ATG and CsA compared to Rabbit ATG and CsA in patients 2 years or older with treatment-naive Aplastic Anemia. This study encompassed 120 participants divided evenly into 60 patients per arm: 60 patients would receive Horse ATG and CsA (the treatment group) while the remaining 60 would receive Rabbit ATG and CsA. This study presented a variety of outcomes, but this evidence based medicine review will focus on the patient oriented outcome of overall survival. Survival was measured at 3 years post-ATG therapy using the Kaplan Meier curve for overall survival. The Kaplan Meier curve data was determined based on hematologic response at 6 months after ATG therapy in both groups. The extent of hematologic response was determined based on the return of blood counts to within normal ranges and having patients become transfusion-independent. Overall survival at 3 years significantly differed between the two treatment regimens as is evident from their respective confidence intervals: 96% of patients survived in the Horse ATG and CsA group whilst only 76% of patients survived in the Rabbit ATG and CsA group. As calculated by the results of the study, for every 5 patients receiving horse ATG plus CsA, 1 more patient is going to survive than if Rabbit ATG plus CsA was given initially (refer to Table 2 for NNT value). The difference between the two groups was

represented with a p-value of 0.04, making the data reported in this study statistically significant, and Horse ATG plus CsA the superior treatment option.

Table 2: Clinical Efficacy of Using Horse ATG plus CsA to treat Aplastic Anemia

Study	CER (rATG)	EER (hATG)	RBI	ABI	NNT
Scheinberg et al	76%	96%	26.3%	20%	5

CER – control event rate; EER – experimental event rate; RBI – relative benefit increase; ABI – absolute benefit increase; rATG – rabbit ATG; hATG – horse ATG

Passweg et al<sup>5</sup> is a randomized control trial which assessed the efficacy of Horse ATG and CsA compared to Basic Supportive Care (BSC) in patients older than eighteen years of age with a documented MDS diagnosis. This study encompassed 88 participants, 45 of which were randomly assigned to receive Horse ATG and CsA while the remaining 43 were randomly assigned to receive BSC. In this study, patients were permitted to cross over from the BSC group to the Horse ATG and CsA group if their MDS progressed to a more advanced stage or if they did not have a response with BSC after 6 months. This study qualified as a randomized control trial because patients were randomly assigned to their respective treatment arms. The patient oriented outcome measured in this study was overall survival, defined as “the time from trial registration until death as a result of any cause.”<sup>2</sup> Overall survival was measured 2 years after treatment was administered. There was not much variability in the confidence intervals of overall survival for the respective treatment groups, as a total of 40 deaths had occurred throughout the study: 49% of the patients in the Horse ATG and CsA arm had survived, while 63% of the patients in the BSC arm had survived. The difference between the two groups was represented with a p-value of 0.828. As calculated by the results of the study, for every 7 patients receiving horse ATG plus CsA, 1 fewer patient is going to survive than if BSC was given initially (refer to Table 3 for NNT value). Thus, based on the p-value and confidence intervals reported in this

study, there is no statistically significant difference between the use of Horse ATG plus CsA or BSC in MDS patients as it pertains to 2-year survival.

Table 3: Clinical Efficacy of Using Horse ATG plus CsA to treat patients with MDS

Study	CER (BSC)	EER (hATG)	RBI	ABI	NNT
Passweg et al	63%	49%	-22.2%	-14%	-7

Shin et al<sup>6</sup> is a single-center retrospective study which assessed the efficacy of Horse ATG and CsA compared to Rabbit ATG and CsA in patients older than 15 years who received Horse or Rabbit ATG as a first-line therapy for Aplastic Anemia. This study retrospectively analyzed 99 participants, 46 of which were treated with Horse ATG plus CsA, while the remaining 53 were treated with Rabbit ATG plus CsA. There were two patient-oriented outcomes presented in the results including overall survival and failure free survival. Both of the survival data was measured at 5 years post-ATG therapy using the Kaplan Meier curve for overall survival. The Kaplan Meier curve data was determined based on the patient’s overall complete hematologic response at 3, 6, 12, and 18 months after ATG therapy in both groups. The extent of hematologic response was determined based on the return of blood counts to within normal ranges and having patients become transfusion-independent. Overall survival and failure free survival at 5 years did not display a significant difference between the two groups, which is evident by the respective p-values: 0.460 for overall survival and 0.911 for failure free survival. As calculated by the results of the study, for every 125 patients who received horse ATG plus CsA, 1 more patient is going to survive overall than if Rabbit ATG plus CsA was given initially (refer to Table 4 for NNT value). With the outcome of failure free survival, for every 6 patients who received horse ATG plus CsA, 1 more patient will relapse or require additional systemic therapy than if rabbit ATG plus CsA was given initially. Therefore, there is no statistically

significant difference between the use of Horse ATG plus CsA or Rabbit ATG plus CsA in Aplastic Anemia patients as it pertains to 5-year overall and failure free survival.

Table 4: Retrospective Clinical Analysis of Using Horse ATG plus CsA to treat patients with Aplastic Anemia – Overall Survival and Failure Free Survival

	CER (rATG)	EER (hATG)	RBI	ABI	NNT
Overall Survival	82.7%	83.5%	0.967%	0.8%	125
Failure Free Survival	40.9%	26.1%	-36.2%	-14.8%	-6

## DISCUSSION

Antithymocyte globulin (ATG) is a polyclonal immunoglobulin in which the antibodies react with multiple T cell markers and other tissue antigens in order to induce immunosuppression.<sup>5,7</sup> It is believed that ATG works by decreasing the circulating T cells while simultaneously regulating T cell activation.<sup>2</sup> ATG is also very commonly used in combination with other immunosuppressive agents, such as Cyclosporine, in order to increase its efficacy (livertox). ATG is manufactured from the plasma of rabbits or horses which is then immunized with human T cells. Both Horse and Rabbit ATG are FDA approved<sup>2</sup> and commercially available for use in the United States. ATG has been approved for use as an anti-rejection agent in solid organ transplantation and as immunosuppressive therapy for Aplastic Anemia. There are also a number off-label uses for ATG therapy,<sup>7</sup> including its use in low to intermediate risk MDS patients.<sup>5</sup> When first administered, ATG can cause multiple side effects due to a variety of reasons: the patient’s underlying condition, a foreign body immune response due to the animal product component, or initial T cell encounter with the ATG antibodies within the first few days of therapy. Side effects include serum sickness, anaphylaxis, high fever, dyspnea, nausea, chest pain, and diarrhea.<sup>7</sup>

While this selective Evidence Based Medicine review addresses the broader question of whether or not Horse ATG is the best initial therapy for patients with bone marrow failure disorders, the three studies included in this review actually address a further dimension to this question: ATG therapy as initial treatment for patients who do not qualify for bone marrow or stem cell transplantation. Each of the three studies displayed some evidence supporting ATG as a first line therapy for patients who do not initially qualify for transplantation at the time of diagnosis. Passweg et al reports that “stem cell transplantation is the only curative approach, but is not feasible for most patients.”<sup>5</sup> Therefore, this paper is reviewing the secondary treatment option of Horse ATG plus CsA to transplantation for this patient population as another potentially curative approach.

Although the data reported in each of the three studies demonstrated a varying degree of statistical significance, there were small discrepancies which could have ultimately impacted the results. In the Passweg et al<sup>5</sup> study, one major limitation was the lack of an active comparator. With an active comparator, the study was only able to establish that Horse ATG plus CsA was better than no treatment at all, despite there being other immunosuppressive treatments available. Another limitation, present in all of the involved studies, was the relatively small patient population. However, the rarity of these diseases would make it rather difficult to conduct a traditional large-scale study.

## CONCLUSION

Scheinberg et al<sup>4</sup> was the only one of the three studies presented in this selective Evidence Based Medicine review that successfully supported the ultimate question. It demonstrated that Horse ATG was, in fact, the superior immunosuppressive treatment of choice for patients with bone marrow failure disorders who did not qualify for transplantation at the

time of diagnosis. The remaining two articles provided inconclusive data regarding overall survival where the depicted p-values represented insignificant results between Horse ATG plus CsA compared to another treatment modality, including BSC and Rabbit ATG plus CsA.<sup>5,6</sup> Due to the inconsistency with data across the spectrum of these studies, further research would be warranted to determine the initial immunosuppressive treatment of choice for patients with bone marrow failure disorders who do not qualify for transplantation. In the future, it would also be useful to create a study which compares the initial and superior immunosuppressive treatment to transplantation in order to assess the overall efficacies of both treatment modalities. Therefore, patients could ultimately benefit by weighing the benefits and risks of each treatment option.

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