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Research Article

A Secondary Data Analysis on Effectiveness of Gamma Interferon Therapy in Chronic Granulomatous Disease (CGD) Patients Using a Randomized Controlled Trial Data

Muhammad Soomar S*
Department of Community Health Sciences, Aga Khan University, Pakistan

***Corresponding author:** Muhammad Soomar S, Department of Community Health Sciences, Aga Khan University, Pakistan

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Abstract

Background: Chronic Granulomatous Disease (CGD) is a group of inherited rare disorders of the immune function characterized by recurrent pyogenic infections which usually present early in life and may lead to death in childhood. Phagocytes from CGD patients ingest microorganisms normally but fail to kill them, primarily due to the inability to generate a respiratory burst dependent on the production of superoxide and other toxic oxygen metabolites. Thus, it is the failure to generate microbicidal oxygen metabolites within the phagocytes of CGD patients which confers the greatly increased susceptibility to these severe or even life-threatening infections. There is evidence establishing a role for gamma interferon as an important macrophage activating factor which could restore superoxide anion production and bacterial killing by phagocytes in CGD patients.

Methods: A double blinded randomized controlled trail to determine the effectiveness of gamma interferon therapy in patients who had a confirmed diagnosis of CGD before the study. Participants were 203 patients from 13 centers of 4 countries from United States and Europe. The effectiveness of gamma interferon therapy was analyzed using Weibull distribution parametric survival regression model.

Results: Twenty four percent of patients who received treatment with interferon developed serious infection and forty six percent developed serious infections among those who received placebo. The survival time with gamma interferon is two times better than those who received placebo. The survival time of males with auto recessive inheritance was low as compared to females with Autoreccesive inheritance.

Conclusion: The current study provides the evidence that gamma interferon therapy proved to be effective in treating patients with Chronic Granulomatous disease and males are more at risk of developing CGD with any genetic type compared to females. Clinicians and physicians can use gamma interferon therapy to treat patients with CGD as it has proved to be effective in reducing the infections and increasing the survival time.

Abbreviations

CGD: Chronic Granulomatous Disease; US: United States

Introduction

Chronic Granulomatous Disease (CGD) is an inherited rare disorder of phagocytes occurring in one in 250,000 population [1]. It is the defect of Nicotinamide-Adenine-Dinucleotide-Phosphate (NADPH) oxidase complex in phagocytes specially in neutrophils and monocytes which cause functional impairment of these phagocytes to kill the foreign particle entering in the body and causing recurrent infections. CGD patients are susceptible to bacterial and fungal infections [2,3].

CGD is usually present early in life and may lead to death in childhood if there is no initial diagnosis and treatment [4]. Normally Phagocytes from CGD patients ingest microorganisms i.e. bacteria and fungi but due to the disorder phagocytes fail to kill them, primarily due to the inability to generate a respiratory burst dependent on the production of superoxide and other toxic oxygen metabolites [5]. Thus, it is the failure to generate microbicidal oxygen metabolites within the phagocytes of CGD patients which causes the greatly increased susceptibility to these severe or even life-threatening infections [6].

CGD may be present at any age but majority of the patients are diagnosed at less than 5 years of age and most of the patients by 10 years of age [7]. There was no evidence about this rare inherited disorder until 1950s, the disease was initially known as fatal disease of childhood, it was well characterized in 1959 as disease causing

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the recurrent infections which lead to hypergammaglobulinemia (increased level of immunoglobulin in blood serum) [8]. Originally it was thought that this disease is X-linked disease and appeared only in males, but the later advancement and researches determines its autosomal recessive forms and females were affected from this disorder as well but a greater ratio of this disease was found to be in males [1].

Globally the mortality rate from CGD in patients with X-linked inheritance is 5% per year whereas the mortality rate in patients with autosomal recessive inheritance is 2% per year however the mortality rate has been ranging between 2-5% per year in the United States. Moreover, the advancements have also led to the management of the disease and marked an improvement in the life expectancy [2,9].

The survival of the patients with CGD is largely associated with superoxide production regardless of the specific gene affected. Recent studies have reported that survival rate of patients have improved with the early diagnosis of the disease and the therapies used for the treatment of the disease [10]. There is evidence of establishing a role for gamma interferon as an important macrophage activating factor which could restore superoxide anion production and bacterial killing by phagocytes in CGD patients [11]. This study aims to determine the effectiveness of gamma interferon therapy in patients with Chronic Granulomatous Disease.

Methods

Study design and setting

The CGD study, which is described in a report by the International CGD Cooperative Study Group (1991) is a randomized double blinded, placebo-controlled trial was designed to determine whether the gamma interferon could decrease the frequency and severity of serious infections and improve chronic infectious condition in patients with Chronic Granulomatous Disease having any type of genetic inheritance. Patients were randomly assigned to treatment through a randomization scheme. This trial includes 13 centers at 4 countries in United States and Europe (Group*, 1991).

Study population

Participants of the study enrolled were those who had a confirmed diagnosis of CGD before the study. The diagnosis was based on the medical condition and laboratory testing i.e. "abnormal results of neutrophil nitro blue tetrazolium and neutrophil superoxide production no more than 20% of the normal." The other criteria for eligibility included "preserved renal, hepatic, and hematologic function, a minimum life expectancy of 3 months." Informed consent was taken prior to study from their parents or guardians (Group*, 1991).

Sample Size

Sample size was 203, patients from all the 13 centers of 4 countries in United States (US) and Europe. 83 patients received interferon and 120 patients received placebo.

Enrollment of Participants

Between October 1988 and March 1989, 128 eligible patients with CGD were accrued by the International CGD Cooperative Study Group from all the 13 centers of 4 countries in United States and Europe. Since the study required delivering placebo injections three times weekly for a twelve-month period to one-half of the patients, most being children, there was particular interest in achieving early termination of the trial if early results were extreme. A single interim analysis was to be performed as soon as patient follow-up was available through July 1989, six-months after the date on which one-half of the patients had been accrued.

Data collection

The primary end point of the study was the time to serious infection, the time to the first serious infection was recorded in days between the date of random assignment to the treatment and the date of diagnosis of serious infection. The patients received interferon gamma or placebo by subcutaneous injection three times weekly on alternate days i.e. on Monday, Wednesday, and Friday for up to 12 months unless unacceptable toxicity was observed. Careful monitoring of patients through laboratory evidence of toxicity related to gamma interferon. Toxicity was graded according to criteria specified in the protocol. (Group*, 1991).

Data analysis

This secondary data analysis was done using STATA version 16.0. The descriptive analysis of all independent variables and outcome variable was done. All normally distributed continuous variables were summarized with their mean and standard deviation. For categorical variables, frequency counts and percentage were reported. Kaplan Meier estimates for survival function were obtained and log rank test was to compare the survival distributions. Weibull distribution parametric survival regression model was employed to do the analysis of this study. Univariate analysis was done initially to assess the significance of variables, admissibility in the multivariable model was at significance level of <0.25. Furthermore, before progressing to multivariable analysis, multicollinearity bestween variables was checked. Variables which were significant on univariate level with no multicollinearity were tested on multivariable analysis at the cut off point for p value <0.05. Assessment of proportionality was done using Global test. Presence of interaction was also assessed in the final model.

Results

The results of this study indicated that 76 patients developed serious infection which constituted 37.43% of the total sample and 127 (62.57%) patients were censored (taken off study).

The baseline characteristics of the participants reported based on the outcome (developed infection or censored) are displayed in (Table 1). The mean age of participants in this study was 13.70 years. Among those who developed serious infection, 65 (38.69%) were males and 11 (31.43%) were females, suggesting that males are more likely to suffer from serious infections due to CGD. 46 (35.11%) of those who developed serious infections were having X-linked pattern of inheritance and 30 (41.67%) have autosomal recessive inheritance pattern. Among those who developed serious infections, 4 (57.14%) individuals used corticosteroids at the time of study entry and 62 (36.05%) used prophylactic antibiotics at the time of study entry.

The development of outcome during the course of study in those who received any type of treatment are exhibited in (Table 2). The results indicated that 83 (40.88%) patients who received treatment with interferon, 20 (24.10%) among those developed serious infection

Table 1: Baseline characteristics of key indicators of participants by outcome (developed serious infection or censored).

Baseline Characteristics	Total n=203	Number of patients with infection 76 (37.43%)	Number of patients Censored 127 (62.56%)
Age*	13.70(0.65) *	12.19 (0.94) *	14.60 (0.87) *
Gender			
Male	168(82.76)	65 (38.69)	103 (61.31)
Female	35(17.24)	11 (31.43)	24(68.57)
Pattern of inheritance			
X-linked	131 (64.53)	46 (35.11)	85 (64.89)
Autoreccesive	72 (35.47)	30 (41.67)	42 (58.33)
Using Corticosteroid			
Yes	7 (3.45)	4 (57.14)	3 (42.86)
No	196 (96.55)	72 (36.73)	124 (63.27)
Using Antibiotics			
Yes	172 (84.73)	62 (36.04)	110 (63.95)
No	31 (15.27)	14 (45.16)	17 (54.83)

(* Means (Standard Deviation))

Table 2: Treatment indicator of participants by outcome (developed serious infection or censored).

Baseline Characteristics	Total n=203	Number of patients with infection 76 (37.43%)	Number of patients Censored 127 (62.56%)
Treatment			
Gamma Interferon	83 (40.88)	20 (24.10)	63 (75.90)
Placebo	120 (59.11)	56 (46.66)	64 (53.33)

Table 3: Weibull distribution parametric model reporting adjusted time ratio with 95% Confidence interval for covariates associated with survival from chronic granulomatous disease.

Characteristics	Crude Time Ratio	95% CI	Adjusted Time Ratio	95% CI
Treatment (Gamma Interferon)	**1.87**	**1.26-2.78**	**1.74**	**1.18- 2.57**
Age	**1.01**	**0.99-1.03**	**1.02**	**1.00- 1.05**
Gender and Pattern of inheritance				
• Female with X-linked inheritance	-	-	-	-
• Male with X-linked inheritance	-	-	-	-
• Female with Autoreccesive inheritance	-	-	**2.92**	**2.45- 3.39**
• Male with Autoreccesive inheritance	-	-	**0.65**	**0.44- 0.96**

and 120 (75.9%) received placebo 56 (46.67%) developed serious infection.

The results of analysis of Multivariable Weibull distribution parametric survival regression model, assessing the association between type of treatment received and development of serious infection, are given in (Table 3). Gender and pattern of inheritance were significantly associated with the development of serious infections due to CGD. The survival rate of Chronic Granulomatous infection in patients received gamma interferon is 1.76 times as compared to patients receiving placebo (TR: 1.76, CI 1.18-2.57). Likewise, with every year increase in age of patients the survival rate of Chronic Granulomatous infection in patients received gamma interferon is 1.02 times as compared to patients who received placebo (TR: 1.02, CI 1.00-1.05).

The final model indicated a significant interaction between gender and pattern of inheritance suggesting that the survival rate of Chronic Granulomatous infection in males with Autoreccesive inheritance is 0.65 times compared to males with X-linked inheritance (TR: 0.65, CI 0.44-0.96).

Discussion

In this placebo-controlled double blinded trial, gamma interferon injections three times a week which reduced the frequency of serious infections in patients with chronic granulomatous disease. Gamma interferon was helpful irrespective of the baseline characteristics i.e. pattern of inheritance of disease, age, or used or not used prophylactic antibiotics. Patients receiving interferon had a decrease in developing serious infection and survival time was increased.

Children less than 10 years of age benefit most from gamma interferon treatment and had fewer side effects with increasing age the survival rate has increased until 90% with timely diagnosis and treatment [12]. Chronic granulomatous disease is often diagnosed during the early years of life, it is significant that the treatment was well effective in patients of early age group. The treatment was associated with instabilities in growth and development in the participants who receive gamma interferon [5].

Gamma interferon therapy was effective in all types of inheritance i.e. X-linked and Autoreccesive of chronic granulomatous disease [13]. This study shows that interferon gamma is an effective and safe therapy for patients with chronic granulomatous disease since the therapy significantly reduced the frequency of serious infections. The results suggest the recommendation that interferon gamma be given to these patients as prophylaxis against infections.

Conclusion

The findings of this study demonstrated the role of gamma interferon therapy in improving the survival rate of patients with Chronic Granulomatous disease. The findings in the literature are extremely consistent with this perception and emphasizes on the need for the treatment of CGD patients with gamma interferon. The results

of this study also indicated that males are more vulnerable to develop chronic granulomatous infection with any type of inheritance. Results of this study also exhibited the interaction between gender and pattern of inheritance which shows that the survival rate of male patients with autosomal recessive inheritance have low survival rate as compared to females. The results also suggest the need for clinicians and physicians to be well aware about this rare inherited disorder and treatment options so that the patients presenting with CGD can be appropriately treated.

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Author's Contribution

All authors have contributed equally.

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