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The Beneficial Effect of 3-Month-Induction Therapy with Corticosteroids and Mycophenolate Mofetil Followed by Maintenance Therapy with Yearly Rituximab Infusions as Sole Maintenance Therapy in Cryptogenic Chronic Hypersensitivity Pneumonitis

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Abstract

Background: The available data on cryptogenic chronic hypersensitivity pneumonitis (ccHP) indicate an inherited predisposition to disease with triggering autoimmune phenomena. Hence, we evaluated prospectively the role of a new autoimmune regimen in treatment of its severe and progressive disease. **Patients and Methods**: A total of 9 patients were included in the study. They had criteria for ccHP viz. 1) clinical features of cryptogenic progressive restrictive lung disease, 2) high-resolution computed tomographic pulmonary abnormalities, and 3) bronchoalveolar lavage lymphocytosis (>30%). The regimen consisted of an initial induction phase of 3-month Solumedrol 1 g IV daily for 3 days followed by 1 month of Prednisone (P) 60 mg/day to tapered down to discontinuation by 3rd month. They also had received Mycophenolate mofetil (MMF) 1 g twice daily for 3 months. This stage was followed by a maintenance phase of yearly Rituximab infusions (1 g followed by 1 g 2 weeks later). **Results**: compared to their previous 6 months deterioration; all patients showed significant improvement in their forced vital volume, diffusion capacity for carbon monoxide, 6-minutes-walk after the induction phase (at 3 months) which improved further at 15 months with Rituximab therapy.

Conclusion: After 3-month induction therapy with P and MMF; yearly R treatment is a safe, practical and effective long-term therapy for ccHP.

Keywords

Hypersensitivity Pneumonitis, Mycophenolate Mofetil, Rituximab, Spirometry, HRCT, BAL

1. Introduction

Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease resulting from exposure to inhaled environmental antigens [1]. In the acute form; a definite inciting antigen (IA) is evident and avoidance with/without short course of corticosteroids is sufficient. On the other hand; the chronic form lacks overt and definite IA, in nearly two-thirds of cases *i.e.*, cryptogenic chronic HP (ccHP) [2]. Unfortunately, the course of the latter is insidious and may progress to lung fibrosis simulating idiopathic pulmonary fibrosis (IPF) [3]. Clinical diagnosis can be made by a combination of; 1) history of progressive dyspnea with/without exposure to IA, 2) pulmonary function tests, 3) BAL cytology, 4) HRCT of chest, 5) transbronchial and/or surgical lung biopsy [4]. Methodological differences may account for the variations in reported incidence and prevalence. However, in a recent large-population study, the calculated yearly incidence rate was 1.28 - 1.94 per 100,000 persons and prevalence at 1.67 - 2.71 per 100,000 persons and the mortality of the progressive fibrotic forms were 28% and 52% after 4 and 7 years, respectively [5]. The age of the reported cases was 52 ± 13 years, and cases were four-times more likely to be men than women [6]. Despite avoidance of IA; ccHP fibrosis may progress [7]. Moreover, Corticosteroids were beneficial only in acute HP not ccHP [7]. Other immunosuppressive agents viz. Azathioprine, mycophenolate mofetil (MMF) had marginal benefit in ccHP had less side-effects than Corticosteroids, yet did not improve survival [8]. Reports on Rituximab (R) therapy of ccHP are scarse yet had shown stabilization of disease [9] [10]. In our current study; we prospectively evaluated a new regimen for treatment of ccHP using an induction phase of Prednisone and MMF for 3 months to suppress the disease activity followed by prevention of future relapses with a maintenance yearly therapy with R.

2. Patients and Methods

Patients were included if they had the following criteria: 1) progressive respiratory failure without occupational or irritant inciting antigen (IA), 2) spirometric evidence of restrictive lung disease and low diffusion capacity of lung for carbon monoxide (DLCO), forced vital capacity (FVC) and 6-minutes-walk (6-MW), 3) absence of chest infections, cardiac disease, primary pulmonary hypertension, collagen vascular diseases, sarcoidosis, lymphoproliferative malignancies, 4) negative past history of drug-induced lung disease, 5) adequate bronchoalveolar

lavage (BAL) showing lymphocytosis (>30%), 6) characteristic pulmonary abnormalities, of ccHP, on high-resolution computed tomography (HRCT), 7) lack of allergy to R infusions, 8) adequate pulmonary function tests showing restrictive pattern, 6-months prior to inclusion and on subsequent follow up for >15 months, and 9) adult age group patients without dementia and morbid obesity.

2.1. Study Design

After control of local and/or systemic infections; patients had received Solumedrol (Methylprednisolone sodium succinate) 1 g infusion, over 1 hour, for 3 days followed by Prednisone 60 mg/day for 1 month that was tapered down and discontinued by 6 weeks. During those initial 3-month-induction period; they had received Mycophenolate mofetil (MMF) 1 g twice daily. On conclusion of the induction period, they had received 1 g of Rituximab infusion, over 4 - 6 hours, followed by another 1 g 2 weeks later. Proton pump inhibitors were used to protect the stomach from ulcerations and bleed.

2.2. Protocol of R Infusions

R (mabthera) infusions were given as a 1 g followed by another 1g two weeks later. Patients were pre-medicated with two 500 mg Paracetamol and one Piriton tablets followed by an infusion of 125 mg of Solumedrol in 50 mL of D5W over 30 min before infusions. Then, 1 g of R was diluted in 400 mL of normal saline leading to a concentration of 2 mg/ml. The first infusion rate was 20 ml/h for the first 30 min, followed by 20 ml increment/h every 30 min till the total dose was achieved. Infusions were discontinued if serious allergic reactions develop.

2.3. Periodic Assessment

Patients were seen every month during the induction phase, then every two months subsequently. In those visits, patients were assessed clinically and by laboratory testing. The latter included; complete blood count and serum estimates of glucose, renal, liver and lipid function tests and urine routine. Moreover, in the first year, flow cytometry was used to separate mononuclear cells and then immunophenotyping was done via staining with antibodies against cell markers. Depletion of B-cells was considered if CD20 was <0.5% of the total lymphocytes [11].

2.4. Assessment of ccHP Response to Therapy

Pulmonary function tests (FVC, and DLCO and 6-MW) were available for all patients 6 months prior to inclusion and subsequently; they were done at time 0, 3 and 15 months. Moreover, repeat HRCT was done after 15 months.

2.5. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value < 0.05 was used as the cut-off level for significance. Since age and duration of prior disease and duration of follow up after R therapy were normally distributed; they were expressed as mean + SD. One-way ANOVA was used to

test significant changes with time in repeated measurements.

3. Results

A total of 9 patients were included in the study of which 2 were females. Their; 1) mean age was 64 ± 2 years, 2) prior duration of disease at 93 ± 7 months, and duration of follow up at 26 ± 7 months.

3.1. Lymphocyte Subpopulation

Subsequent to the initial 2 g R infusions, none of the patients had decline in the total circulating lymphocyte counts, yet all had achieved decline of their initially normal CD19 to <0.5% one month later. The decline persisted for eight months later and had recovered by the 12th month.

3.2. Initial Assessment Prior to Therapy

The data is summarized in Table 1. All patients had moderate disease prior to inclusion that had shown significant deterioration with progressive decline in FVC, DLCO and 6-MW at time 0 compared to -6 months.

3.3. Response to Therapy

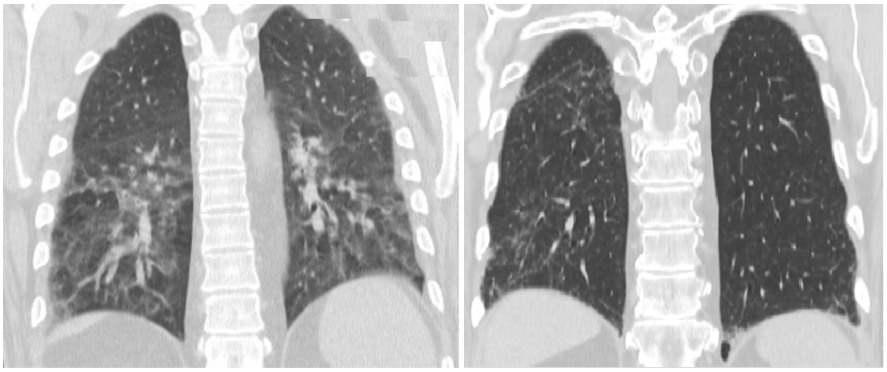
1) On pulmonary function testing; all patients showed restrictive pattern without obstruction (Normal FEV1/VC). Significant improvements ($p < 0.00001$) in FVC, DLCO and 6-MW after the induction phase therapy by 3 months and had improved further after R treatment by 15 months ($p < 0.0.01$, 0.00004 and 0.01) in those respective parameters (Table 1).

2) Repeat HRCT showed significant improvement at 15 months (Figure 1(b), Figure 2(b) compared to Figure 1(a), Figure 2(a)) at start. The initial bilateral, mosaic, ground glass opacities in the middle and lower lung zones and ill-defined centrilobular nodules disappeared and were replaced with few lung reticulations.

Table 1. Time changes in respiratory indices following Rituximab therapy.

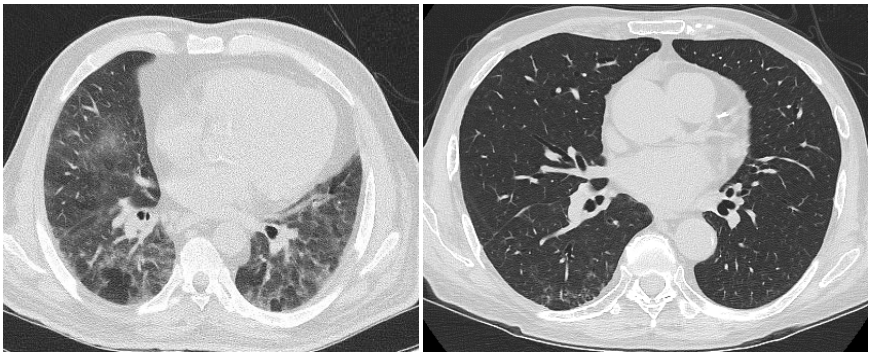
	Time changes*			
Parameters	M-6	M0	M3	M15
DLCO (% of predicted)	62 ± 2	57 ± 2	70 ± 3	72 ± 1
[% change]	[+9]	[0]	[+23]	[+26]
FVC (% of predicted)	67 ± 2	60 ± 3	72 ± 2	75 ± 1
[% change]	[+12]	[0]	[+20]	[+25]
6-MW (meters)	506 ± 28	441 ± 18	550 ± 52	587 ± 29
[% change]	[+15]	[0]	[+25]	[+33]

Abbreviations: DLCO: Diffusion capacity of lung for carbon monoxide, FVC: Forced vital capacity, 6MW: 6-minutes walk; Times of testing: M-6 (6 months prior to therapy), M0: at start, M3: 3 months later, M15: 15 months later; [% change]: changes in each parameter with time relative to M-0; * Significant changes between individual changes with time ($p < 0.00001$) except between M3 & M15 (0.01).



(a) (b)

Figure 1. Coronal CT view showing significant bilateral, mosaic, ground glass opacities in the lower lung zones prior to Rituximab therapy (a) and improvement with just residual fine reticulation on the right posterior segments after therapy (b).



(a) (b)

Figure 2. Axial CT view showing significant bilateral, mosaic, ground glass opacities in the middle lung zones prior to Rituximab therapy (a) and improvement with just residual fine reticulation on the right posterior segments after therapy (b).

3.4. Adverse Events

Immediate infusion-related symptoms included itching, hypotension and bronchospasm. They were mild with; 1) pre-medication with corticosteroids, diphenhydramine and acetaminophen, 2) slowing further the infusion rate. In 1 patient, who could not tolerate the initial infusion schedule, the 2 g R dose was divided into 500 mg weekly infusions over 4 weeks. There were no significant laboratory abnormalities and none of the patients had developed posterior leukoencephalopathy.

4. Discussion

Hypersensitivity pneumonitis (HP) is the third most common interstitial lung disease after idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. However, it remains a challenging condition to diagnose and manage because of its heterogenous clinical, radiologic, histologic and functional features [12]. Clinical diagnosis can be made by a combination of; 1) history of progressive dyspnea with/without exposure to IA, 2) pulmonary function tests, 3) BAL

cytology, 4) HRCT of chest, 5) transbronchial and/or surgical lung biopsy [4]. Details include; 1) Common exposures to IA viz. Low-molecular weight chemicals (42.7%) and animal proteins (37.5%), 2) restrictive lung impairment (low FVC and 6-MW) with poor DLCO, 3) BAL cytology should rule out inflammatory, infectious and malignant etiologies and shows > 30% lymphocytosis, 4) HRCT chest abnormalities viz. bilateral, mosaic, ground glass opacities in the middle and lower lung zones (64.6%), ill-defined centrilobular nodules (29.9%) and the sign of air-trapping on expiration (15.6%) in acute/subacute phase while reticulation (45.8%), traction bronchiectasis (21.9%) and honey combing (9.4%) in chronic disease, 5) histological abnormalities on biopsy viz. peribronchiolar diffuse interstitial inflammatory infiltrates, chronic bronchiolitis and peribronchiolar giant cells (with or without non-caseous and non-necrotic granulomas). In our study, none of our patients had identifiable IA *i.e.*, cryptogenic ccHP yet all had typical abnormalities on chest HRCT as per recommendations of CHEST guidelines [5]. Moreover, we added testing for BAL lymphocytosis to satisfy criteria for ATS/JRS/ALAT guidelines [13]. Inflammation in ccHP is mediated by both humoral and cellular mechanisms. The IA activates T-helper lymphocytes followed by activation of B-lymphocytes and subsequent release of antigen-specific immunoglobulin (Ig) G antibodies that leads to accumulation of lymphocytes and formation of granulomas. The fibrotic disease is due to the abnormal repair mechanisms following recurrent alveolar epithelial injury leading to fibroblast activation and proliferation, the accumulation of extracellular matrix, and the eventual destruction of the lung architecture [1]. Hence, treatment of ccHP should start with a short course of aggressive and specific immunosuppressive drugs to halting the active inflammation which was in our patients was evident with 1) disease progression over prior 6 months, and 2) persistent HRCT abnormalities, and 3) high lymphocytic counts in BAL. Subsequently, suppression of activated B-cells, with potent, practical and safe long-term drug, should provide proper maintenance therapy. Hence, in our study we used 2 potent antiproliferative (cytotoxic) agents viz. P & MMF were used simultaneously to treat active ccHP (induction phase) since multiple effector cells are involved. Subsequently, to prevent future relapse, R was used since it is a potent cytotoxic agent to mature B-lymphocytes.

This potent chemo-therapeutic effect is associated with good tolerability profile yet with mild to moderate infusion reactions; hence, it has to be administered slowly over hours, especially the first time [14]. The latter is much less than that observed in treatment of lymphoma which is associated with greater degree of cytokine release [15]. Previously, we reported our experience with the efficacy and safety of yearly Rituximab infusions in many autoimmune diseases [16] [17] [18] [19]. Moreover, the clinical remission induced by R may persist beyond the effect of peripheral B-cell ablation since alteration of memory cells has been reported up to 6 years [20]. The latter character, its long-lasting efficacy (months) and safety were the basis of our protocol for selecting such an agent as a sole maintenance therapy in the second group of our study. Previous studies have

shown benefit of R in just stabilization of ccHP [9] [10]. They did not include an essential induction phase to revert the disease which was evident in the dramatic improvement of our patients by the 3rd month. Previous studies have shown such drugs are effective in treatment of acute inflammatory HP [7] [8]. The effective protocol, in our study, is similar to that used, by our group, in treatment of lupus nephritis [17]. The need for an effective and safe long-term therapy for ccHP is evident with 2 observations. The first is that avoidance of IA may be rewarding in halting early/acute phase of the disease yet is less effective in chronic/fibrotic forms and even can progress despite avoidance of IA [7]. The second is that nearly 2/3 of those with ccHP lack definite IA [2]. These 2 observations indicate that a genetic predisposition to its autoimmune pathogenesis disease is likely. The latter is further supported by the following; for the following reasons; 1) several genetic polymorphisms, including those in major histocompatibility complex class II, have been associated with susceptibility to HP. The MUC5B allele rs35705950 has been associated with a greater extent of radiographic fibrosis, and short telomere length has been associated with worse survival [21], 2) a diffuse Tc1 immune response of lung parenchyma and airways in patients previously sensitized to one of more than 300 etiologic agents that may favor the HP reaction [22], 3) Transporter associated with antigen processing (TAP) 1 gene polymorphisms [23], and 4) several cytokines and chemokines, which are secreted at sites of disease activity, participate in the pulmonary inflammatory responses taking place in the lung of patients with HP [22]. Hence, early long-term safe and effective immunosuppressive therapy is indicated prior to fibrotic stage in susceptible phenotypes in which Nintedanib and Pirfenidone are last resorts otherwise lung transplantation [24] [25]. Finally; the authors acknowledge the limitation of the study with such small number of included patients for such an uncommon disease.

5. Conclusion

Treatment of ccHP with a 3-month induction phase with P & MFF followed by a maintenance yearly therapy with R is practical, safe and efficacious.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki.

There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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