



Original Article

Comparative Study of Oral Azathioprine and Intravenous Cyclophosphamide Pulses in the Treatment of Idiopathic Pulmonary Fibrosis

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ABSTRACT

Introduction: The purpose of the study was to establish the efficacy of treatment with intravenous cyclophosphamide pulses and oral corticoids in idiopathic pulmonary fibrosis, compared with the standard treatment with corticoids and azathioprine.

Patients and methods: A prospective, non-controlled study with 2 parallel groups. One group received prednisone plus oral azathioprine for 24 months (AZA group). The second one (CIC group) received prednisone plus intravenous cyclophosphamide pulses (6 monthly and 6 three-monthly). The primary outcome was survival or period without need for a transplant at 36 months. The secondary outcomes were the forced vital capacity, the carbon monoxide diffusing capacity, and baseline arterial oxygen pressure at 3, 6, 12, 18, 24, 30, and 36 months.

Results: A total of 46 patients were included in the study, of whom 25 were assigned to the AZA group and 21 to the CIC group. The survival or absence of lung transplant at 36 months was 44% in the AZA group and 76% in the CIC group ($p = 0.028$). The forced vital capacity was worse in 8.8% of the AZA group, compared to 6.7% in the CIC group ($p = 0.16$). The carbon monoxide diffusing capacity worsened in 11.81% of patients of the AZA group and in 4.4% of those in the CIC group ($p = 0.0569$). No significant differences were observed in the arterial oxygen pressure. There was one dropout of treatment with prednisone.

Conclusions: Treatment with intravenous cyclophosphamide pulses produced a significant improvement in survival. There were no significant differences in the lung function parameters or gas exchange. Neither of the cytostatics had serious side effects.

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Estudio comparativo entre azatioprina oral y pulsos intravenosos de ciclofosfamida en el tratamiento de la fibrosis pulmonar idiopática

RESUMEN

Introducción: El objetivo del estudio ha sido establecer la eficacia del tratamiento con pulsos intravenosos de ciclofosfamida y corticoides orales en la fibrosis pulmonar idiopática, comparados con el tratamiento estándar con corticoides y azatioprina.

Pacientes y métodos: Estudio prospectivo, no controlado, con 2 grupos paralelos. Un grupo recibió prednisona más azatioprina oral durante 24 meses (grupo AZA). El segundo grupo (grupo CIC) recibió prednisona y pulsos intravenosos de ciclofosfamida (6 mensuales y 6 trimestrales). El objetivo principal fue la supervivencia o período sin necesidad de trasplante a los 36 meses, y los objetivos secundarios, los valores de capacidad vital forzada, capacidad de difusión del monóxido de carbono y presión arterial de oxígeno basalmente y a los 3; 6; 12; 18; 24; 30, y 36 meses.

Resultados: En el estudio se incluyó a 46 pacientes, de los cuales 25 se asignaron al grupo AZA y 21 al grupo CIC. La supervivencia o ausencia de trasplante pulmonar a los 36 meses fue del 44% en el grupo AZA y del 76% en el grupo CIC ($p = 0,028$). La capacidad vital forzada a los 36 meses empeoró un 8,8% en el grupo AZA, frente a un 6,7% en el grupo CIC ($p = 0,16$). La capacidad de difusión del monóxido de carbono empeoró un 11,81% en los pacientes del grupo AZA y un 4,6% en los del grupo CIC ($p = 0,0569$). No se registraron diferencias significativas en la evolución de la presión arterial de oxígeno. Hubo un abandono de tratamiento con prednisona.

Conclusiones: El tratamiento con pulsos intravenosos de ciclofosfamida produjo una mejoría significativa de la supervivencia. No hubo diferencias significativas en los parámetros de función pulmonar e intercambio gaseoso. No se produjeron efectos adversos graves relacionados con ambos citostáticos.

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Palabras clave:

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Tratamiento

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing disease of unknown aetiology, the progression of which leads inexorably to terminal respiratory failure from 2 to 5 years after the first symptoms appear.^{1,2} For 50 years, corticoids have been the cornerstone of treatment, but their efficacy is controversial, given the lack of multi-centre, randomized and placebo-controlled clinical trials.³ The pharmacological treatment, which is currently proposed by various scientific respiratory societies, is a combination of low-dose corticoids with an oral immunodepressant, preferably azathioprine, as it has fewer undesirable effects when used with cyclophosphamide.^{4,5} Treatment with intravenous pulses or boluses of cyclophosphamide, which is widely used in a range of immunological processes, has barely been studied in lung diseases in general and in IPF in particular. The aim of this study was to compare the efficacy and safety of this treatment and standard azathioprine treatment.

Patients and Methods

Patients diagnosed with IPF at our pneumology service from March 2003 to March 2006 were included in the study. Compliance with the consensus criteria of the American Thoracic Society and the European Respiratory Society (ATS/ERS)⁴ was required for the diagnosis of IPF:

1. Patients with typical interstitial pneumonia confirmed by lung biopsy:
 - Exclusion of other known causes of interstitial disease.
 - Changes in the respiratory function evaluation (restrictive ventilation abnormalities) and/or gas exchange abnormalities –an increase in the difference between alveolar oxygen pressure and arterial oxygen pressure (PaO₂) values in a resting state or in effort tests, or a decrease in carbon monoxide diffusion capacity (DLCO).
 - Typical pathological changes in the chest X-ray or high-resolution CT scan.
2. In patients without a lung biopsy, the following 4 major criteria and 3 of the minor criteria must be met:
 - *Major Criteria:* a) exclusion of other known causes of interstitial disease; b) changes in the respiratory function evaluation (restrictive ventilation abnormalities) and/or gas exchange abnormalities (an increase in the difference between alveolar oxygen pressure and PaO₂ values in a resting state or in effort tests, or a decrease in DLCO); c) typical pathological changes in the chest X-ray or high-resolution CT scan and d) a lack of abnormalities in the transbronchial biopsy or bronchoalveolar lavage, which indicate an alternative diagnosis.
 - *Minor criteria:* a) age over 50 years; b) effort dyspnoea of insidious onset which cannot be explained by any other cause; c) symptoms have persisted for more than 3 months or d) persistent bibasal crepitant rales during inhalation.

The first group of patients was treated with prednisone and azathioprine, both of which were administered orally, for a period of 24 months (AZA group). A second group (CIC group) was treated with oral prednisone and intravenous pulses of cyclophosphamide (6 pulses per month followed by 6 pulses every three months). The prednisone dose administered to patients was as follows: 0.5mg/kg/day the first month; 0.25mg/kg/day during the following 2 months; 0.25mg/kg on alternate days from months 3 to 12 and 10mg on alternate days from months 13 to 24. The dose of azathioprine, administered to patients in a single daily dose, was 2mg/kg/day (maximum 150mg/day). Cyclophosphamide was administered at a dose of 750mg/m² surface area. All the patients received N-acetylcysteine on an indefinite basis (1,800mg/day), omeprazole (20

or 40mg/day) and preventive treatment for corticoid-induced osteoporosis consisting of calcium, vitamin D and biphosphonates (alendronate or risedronate administered weekly). Two patients in the CIC group received bosentan to treat “disproportionate” pulmonary hypertension”. Analytical tests were carried out monthly during the first year (haemogram, hepatic and renal profiles) and every 3 months during the second year. In patients in the CIC group, urine sediment assays were conducted every 3 months and urine cytology tests every six months.

The main objective of the study was survival or a 36 month period after starting treatment without the need for a lung transplant. The secondary study variables were: forced vital capacity (FVC), DLCO and PaO₂ at 36 months. Lung function parameters were measured at baseline and at 3; 6; 12; 18; 24; 30 and 36 months.

Undesirable effects related to the treatment were recorded for both groups.

The exclusion criteria were as follows: heart, liver or haematological disease, renal failure, active malignant neoplasia, cognitive decline, epilepsy, previous obstructive pulmonary disease, PaO₂ below 55mmHg at the time of diagnosis and age of 75 years or over.

Statistical Analysis

The continuous variables are presented as the average ± standard deviation. The ² and Fisher's exact test (< 5 cases) were employed for the comparison of qualitative variables. Quantitative variables were compared using the Student's t test. A multivariate analysis was performed by linear regression. Kaplan-Meier survival analysis (logarithmic range) was used for the time variables. A value of p < 0.05 was considered statistically significant. The statistical analysis was conducted using the SPSS for Windows program (version 12).

Results

A total of 46 patients, 25 of whom were assigned to the AZA group and 21 to the CIC group, were included in the study. The baseline characteristics of both groups are shown in table 1.

Survival

A total of 19 patients died or received a lung transplant 36 months after starting treatment (18 deaths and one lung transplant; 14 belonged to the AZA group and 5 to the CIC group), which corresponds to an overall survival rate of 58.7% (44% in the AZA group and 76% in the CIC group; p = 0.028). In the first 12 months 3 patients died, 2 from the AZA group (survival 92%) and one from the CIC group (survival 94.2%; difference insignificant). At 24 months, 8 patients from the AZA group and 2 from the CIC group had died, which represents an accumulated survival of 68 and 90.5% respectively (p = 0.0476). The survival for both groups is shown in fig. 1.

All the patients died from respiratory complications. The causes of death in the AZA group were: 7 patients as a result of progressive respiratory failure, which was attributed to the progression of the disease, 3 of exacerbations of pulmonary fibrosis, 2 of community-acquired pneumonia, one of pleural mesothelioma and one of pleural empyema. For its part, in the CIC group mortality was due to progressive respiratory failure (3 cases) and exacerbation of IPF (one case). One patient received a lung transplant during month 32. The transplant patient and another CIC group patient who died were the only trial participants who received bosentan to treat disproportionate pulmonary hypertension.

In the logistic regression model there were no statistically significant differences in survival rates or in the following variables: sex, age, type of diagnosis (biopsy or other method), FVC and DLCO at the time of diagnosis. Only the type of treatment (p = 0.0176) and a PaO₂ value higher than 65mmHg at the time of diagnosis were

Table 1
Baseline Characteristics of Patients

	AZA Group	CIC Group
Number	5	21
Average age (years)	65 (range: 43-73)	63 (range: 40-73)
Males/females	18/7	11/10
Biopsy/ATS/ERS criteria	13/12	13/8
FVC (% reference value)	76 ± 15%	76 ± 10%
DLCO (% reference value)	68 ± 15%	67 ± 16%
PaO ₂ (mmHg)	66 ± 6	65 ± 5

ATS/ERS: consensus of the American Thoracic Society and the European Respiratory Society; AZA: oral azathioprine; CIC: intravenous pulses of cyclophosphamide; DLCO: carbon monoxide diffusion capacity; FVC: forced vital capacity; PaO₂: arterial oxygen pressure.

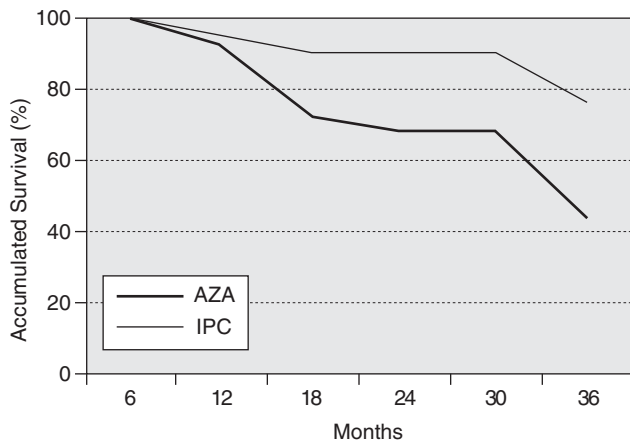


Figure 1. Accumulated Survival in Both Groups. AZA: oral azathioprine; CIC: intravenous pulses of cyclophosphamide.

statistically significant for survival ($p = 0.0255$). Furthermore, for each millimetre of mercury PaO₂ increased over and above 65mmHg at the time of diagnosis, survival time increased 2.93%.

Forced Vital Capacity

The average FVC (± standard deviation) of the surviving patients in the AZA group at 36 months was 67.2 ± 15.3% (baseline difference -36 months = 78.8%), while in the CIC group it was 69.5 ± 12.3 (baseline difference -36 months = -6.7%). The difference between the two groups was not significant ($p = 0.16$). Significant differences between the two groups were not recorded in any of the regular tests that were conducted during the follow-up period.

Figure 2 shows how this pulmonary function parameter evolved over time.

Carbon Monoxide Diffusion Capacity

In patients surviving at 36 months in the AZA group, the DLCO was 55.8 ± 16% (baseline difference -36 months = 71.81%) and in their CIC group counterparts the DLCO was 62.1 ± 17.9% (baseline difference -36 months = 74.4%). Although there was a tendency towards significance, the difference between the two treatment groups did not reach statistical significance ($p = 0.0569$). At the different control points, only the difference in the evaluation performed during month 18 was statistically significant (AZA group: 71%; CIC group: +4%; $p = 0.048$).

How the DLCO evolved over time is shown in figure 3.

Arterial Oxygen Pressure

There were no statistically significant differences between the two groups for the baseline values and the values measured at 36 months: 66 ± 6.2 compared to 64.4 ± 8.3mmHg in the AZA group and 65.9 ± 5.8 as opposed to 62.14 ± 6.48mmHg in the CIC group.

Undesirable Effects

Two patients in the AZA group and one patient in the CIC group developed moderate leukopenia, which was corrected by reducing the dose of both drugs. One patient in the CIC group suffered a migraine which was related to the intravenous pulses. It was not necessary to discontinue the drug in any of these patients. One patient from the AZA group suffered a crushed vertebra in month 9 of the treatment phase, so the corticoid was withdrawn and the treatment was continued with azathioprine only. No cases of liver or lung toxicity, or urinary complications were recorded in either of the 2 groups throughout the study. During follow-up after the study, one patient from the CIC group was diagnosed with cervical carcinoma in situ in the course of a routine gynaecological check-up.

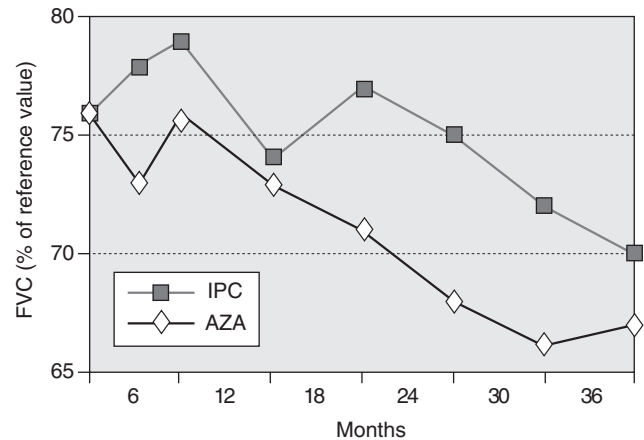


Figure 2. Evolution of Forced Vital Capacity (FVC) in Both Groups. AZA: oral azathioprine; CIC: intravenous pulses of cyclophosphamide.

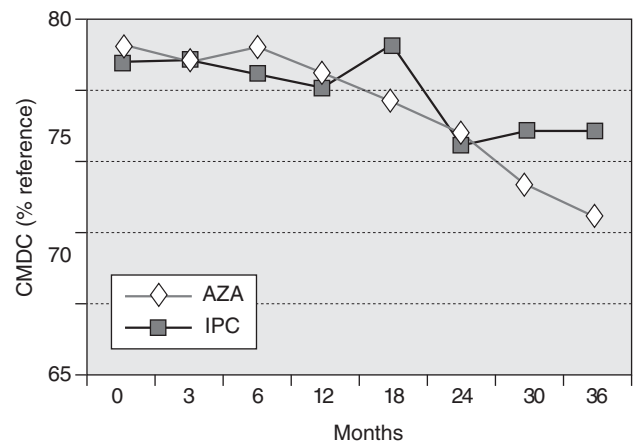


Figure 3. Evolution of Carbon Monoxide Diffusion Capacity (DLCO). AZA: oral azathioprine; CIC: intravenous pulses of cyclophosphamide.

Discussion

If the role of corticoids in IPF is controversial, the role of immunodepressants is even more so. On the basis of research by Johnson et al.⁶ and Raghu et al.,⁷ which showed a slight improvement in the survival of patients treated with cyclophosphamide plus prednisolone, compared to prednisolone alone in the first case, and azathioprine plus prednisone compared to prednisone alone in the second, the ATS/ERS⁴ consensus recommends combined treatment using a corticoid and an immunodepressant. However, the same consensus indicates that there is no evidence, based on properly conducted, randomized and placebo-controlled clinical trials, which demonstrates that combined corticoid-immunodepressant treatment produces an improvement in the survival or quality of life of IPF patients and that the potentially serious adverse effects could have a greater impact than the potential benefits of this therapy. There are retrospective studies which fail to demonstrate benefits in the survival of patients who received combined corticoid-immunodepressant treatment, in comparison with patients who received no pharmacological treatment.⁸ In its review on the efficacy of immunomodulators in the treatment of IPF,⁹ the Cochrane Library indicates that there is little evidence to justify the routine use of non-corticoid agents in the treatment of IPF. It is indicated in the same review that the general quality of the studies which were identified is deficient and that the older immunodepressants (azathioprine and cyclophosphamide) have not been properly evaluated. In addition to the absence of properly executed clinical trials, a second problem is that a fair number of studies were conducted prior to the current classification of idiopathic interstitial pneumonias,¹⁰ so it is likely that heterogeneous diseases and conditions were evaluated.

Cyclophosphamide is an alkylating agent which can be administered orally and intravenously.¹¹ In the latter case it can be administered at low-average daily doses or, alternatively, at high monthly doses (pulses or boluses). Treatment with intravenous boluses of cyclophosphamide is widely used in vasculitis and systemic autoimmune diseases.¹² Its efficacy is greater than oral administration in some processes, such as lupus nephritis or alveolar haemorrhagic syndromes associated with systemic erythematous lupus,¹³ and in the control of immunological diseases which progress very rapidly.¹⁴ Its toxicity is also lower than when it is delivered orally—essentially urological toxicity (haemorrhagic cystitis and carcinoma of the bladder)—, given that the accumulative dose is 6-7 times less in the case of boluses than in the case of oral administration.¹¹

There are very few references to the efficacy and safety of cyclophosphamide boluses in IPF. In a study published in 1992, Baughman y Lower¹⁵ treated 33 patients with fortnightly boluses of cyclophosphamide and prednisolone for a maximum of 18 months. The patients who survived more than 6 months showed a significant improvement in FVC, which was maintained during the following year. In a retrospective study of 18 patients, treated with cyclophosphamide boluses and oral prednisolone for one year Kolb et al.,¹⁶ observed a favourable effect in 11 (stabilization or improvement of FVC and PaO₂). This effect was maintained for at least 3 months after the treatment was withdrawn. However, the two above mentioned studies had no comparative group.

The most interesting study, in our opinion, is one that was carried out by Pereira et al.¹⁷ It is a retrospective comparative study which included 82 patients, 26 of whom received only corticoids and 56 corticoids together with an immunodepressant (oral azathioprine, oral cyclophosphamide or cyclophosphamide boluses). The average survival rate was 25 months for the group given corticoids only and 45 months for the corticoid plus immunodepressant group, a difference which was statistically significant, although it was associated with patients with an FVC higher than 70% of the reference

value when the diagnosis was confirmed. The study does not indicate any differences for the 3 modes of immunodepressant treatment. In our study, the FVC at the time of diagnosis is not a statistically significant parameter of survival. On the other hand, the PaO₂ at the time of diagnosis, with a cut-off point of 65mmHg, does influence survival. In Pereira et al.'s study, the existence of undesirable effects in 8% of the patients, in the corticoid only group and in 29% in the corticoid plus immunodepressant group, is worthy of mention. Cyclophosphamide treatment was interrupted in 6 patients, who suffered haemorrhagic cystitis, fatigue and leukopenia. This data contrasts with the findings in our patients: treatment was only suspended in one patient as a result of a prednisone-related spontaneous vertebral fracture. Both azathioprine and cyclophosphamide were well tolerated. The main adverse effect in our study was the appearance of cervical carcinoma in situ in one patient during the follow-up period after the study, although any link with the therapeutic mode that was employed is open to discussion.

What does stand out in our study is the statistically significant improvement in survival in the second and third years in the CIC group, with respect to the AZA group (although not in the first year). This improvement in survival does not translate, however, into a statistically significant difference in both groups in the pulmonary function and gas exchange tests: only the difference in the DLCO approaches statistical significance and it is significant at a specific stage (month 18 check-up) and is biased in favour of the CIC group. These differences between the objectives of various studies (survival, pulmonary function, radiological score, dyspnoea and quality-of-life indexes) have been reviewed in certain studies¹⁸. Thus, in the first study on the efficacy and safety of pirfenidone, during a one-year follow-up period, significant deterioration was not observed in radiological tests or in PaO₂, but this was not accompanied by a therapeutic effect on survival.^{19,20} The IFIGENIA²¹ study, a multi-centre, randomized trial in which the efficacy and safety of N-acetylcysteine combined with azathioprine and corticoids compared to azathioprine and corticoids alone were studied for one year, a lower rate of decline in pulmonary function (FVC and DLCO) was obtained in the group that received N-acetylcysteine. This beneficial effect on lung function was not associated with an improvement in survival. It is not clear why there is a lack of correspondence between survival and the improvement or loss of pulmonary function.

In conclusion, our results show a significant improvement in survival in patients treated with cyclophosphamide boluses compared to patients who received azathioprine, with very little repercussion on lung function.

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