# LOCAL EXPERIENCE OF PATIENTS WITH CONNECTIVE TISSUE ASSOCIATED INTERSTITIAL LUNG DISEASE WHO WERE TREATED WITH CYCLOPHOSPHAMIDE.

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**Submitted in fulfillment of the requirements for the degree of Master of Medical Science in the school of Clinical Medicine, University of Kwazulu-Natal for a Masters by Research thesis.**

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**Durban, August 2021**

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## DECLARATION :

I, Dr. Swasti Gitesh Singh declare that
(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

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## LIST OF ABBREVIATIONS

CTD – Connective tissue disease

ILD – Interstitial lung disease

CTD-ILD – Connective tissue disease associated interstitial lung disease

CYC – Cyclophosphamide

SSc – Systemic sclerosis

SSc-ILD – Systemic sclerosis associated interstitial lung disease

IPF – Idiopathic pulmonary fibrosis

PHT – Pulmonary hypertension

FVC – Forced vital capacity

FEV1 – Forced expiratory volume in the first second

6MWT – Six minute walk test

DLCO – Diffusing capacity of the lungs for carbon monoxide

HRCT – High resolution computed tomogram

IALCH – Inkosi Albert Luthuli Central Hospital

UIP – Usual Interstitial Pneumonia

NSIP – Nonspecific Interstitial Pneumonia

LIP – Lymphoid Interstitial Pneumonia

BOOP – Bronchiolitis Obliterans Organizing Pneumonia

MCTD – Mixed Connective Tissue Disease

UCTD – Undifferentiated connective tissue disease

PSS – Progressive Systemic Sclerosis

ILA – Interstitial Lung abnormality

KZN – KwaZulu Natal

ESR – Erythrocyte sedimentation rate

CRP – C-reactive protein

WCC – White cell count

HSCT – Haematopoietic stem cell transplantation

MID – Minimal important distance

SA – South Africa

IPAF – Idiopathic Pneumonia with autoimmune features

CTGF – Connective tissue growth factor

EMT – Epithelial-mesenchymal transition

ACR – American College of Rheumatology

EULAR – European League against Rheumatism

CENP – anti-centromere

Topo I – anti-topoisomerase I

RNAP – anti-RNA polymerase III

AA – Autoantibodies

ANA – Antinuclear antibodies

dsDNA – Double stranded DNA

SLB – Surgical lung biopsy

MDD – Multidisciplinary discussion

ATT – American thoracic society

# ABSTRACT

**Introduction:**

Interstitial lung disease (ILD) is a major cause of death amongst individuals with connective tissue diseases (CTD). Although there is no cure for CTD-ILD the need to retard disease progression is vital, hence early detection and treatment is necessary. Cyclophosphamide (CYC) is a potent immunosuppressant that has efficacy in inducing and maintaining remission in autoimmune diseases.

**Objectives:**

The purpose of this study was to assess the clinical, radiological and pulmonary function responses of patients who received intravenous CYC for CTD-ILD at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, Kwa-Zulu Natal, South Africa over a ten year period from January 2009 to December 2018.

**Methodology:**

This was a retrospective electronic chart review conducted at IALCH, the main quaternary public sector hospital in the province of Kwa-Zulu Natal, South Africa. Patients 18 years and older with CTD-ILD treated with CYC were included. Patients were given CYC every 2 weeks for 9 months with a total of 18 doses. Demographic and clinical data, as well as data from special investigations, were captured from medical records. Treatment outcomes were assessed using symptoms, pulmonary function and HRCT changes.

**Results:**

There were 62 subjects, 88.7% being female with the majority between the ages of 40-59 years old (64.5%). Approximately 50% were black Africans followed by ethnic Indians at 43.5% and then Whites at 6.5%. Most patients had Systemic Sclerosis, followed by Mixed Connective Tissue disease and then Systemic Lupus Erythematosus. There was no significant difference in pre and post treatment, symptoms, lung function and HRCT in those who were treated with CYC.

**Conclusion**:

In our setting, the use of 18 doses of CYC every 2 weeks, did not have a significant impact on disease progression.

# CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

## 1.1 Introduction

Interstitial lung disease is a major cause of death amongst individuals with connective tissue diseases. Not all patients with connective tissue associated lung disease develop progressive lung disease. However, a significant number do progress and this leads to reduced physical function, decreased quality of life, and subsequently death. [1] ILD is currently the major cause of death amongst patients with systemic sclerosis.

While the choice of treatment is difficult for these patients it is important to identify those with progressive lung disease and assess the need for immunosuppressive therapy. The potential for adverse effects from highly toxic therapy needs to be weighed against the need for therapy in an unwell patient. [1] Although there is no cure for this disease the need to retard disease progression is vitally important and hence early detection and treatment is required.

The treatment for CTD-ILD is limited to several immunosuppressive agents which generally slow down or halt disease progression. There is limited literature both locally and internationally regarding management and outcomes of patients with CTD-ILD treated with CYC. Internationally, previous research has highlighted the treatment period over 6 months and 12 months. This study focused on local prevalence, demographics and outcomes of patients treated with CYC for the management of CTD-ILD over a nine month period. We aimed to study the effects of CYC pre and post treatment and report our own experiences and compare with studies from other countries.

**Table 1 : Data comparing the findings of the current study with those from other countries**

| | No of patients | No of doses | Most common HRCT pattern | 5 year survival rate (%) |
|---|---|---|---|---|
| This study | 62 | 18 | UIP | 95 |
| Other countries | 55 - >200 | 6-24 | NSIP | 82-90 |

## 1.2 Literature review

### *1.2.1 Interstitial Lung Disease*

Interstitial lung disease (ILD) and diffuse parenchymal lung disease are synonymous terms for a broad range of diseases that involve inflammation and fibrosis of the alveoli, distal airways, and septal interstitium of the lungs.[2]

ILD involves multiple disease entities in respiratory medicine, hence other medical conditions need to be considered in the differential diagnosis of ILD. Some of these diseases include chronic pulmonary oedema, infection, neoplasms, systemic diseases, drug reactions. ILD may occur in elderly patients with multiple co-morbidities.[3] In some conditions like idiopathic pulmonary fibrosis (IPF) the aetiology is unknown.

The diagnosis of ILD depends on clinical findings, pulmonary function tests and high-resolution computed tomography (HRCT).[2] In some patients, a lung biopsy may be required to determine the aetiology of ILD. The histopathological classification has allowed for more precise definition of some disease processes (Table 2). In turn, this classification has assisted

with determining the treatment response and prognosis. When there is a similar pattern of inflammation and fibrosis, this may indicate a response to similar insults. On the other hand, drugs such as amiodarone may affect the lungs in various ways. It is important to distinguish between the histopathological pattern on biopsy and the clinical diagnosis. Therefore the amalgamation of clinical, radiological and histopathological features entails a multidisciplinary approach to diagnosis, treatment and long term follow up. [3]

**Table 2: Classification of interstitial/diffuse parenchymal lung disease**

**Idiopathic interstitial pneumonias**

- Idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP)
- Non-specific interstitial pneumonia (NSIP)
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis/interstitial lung disease (RB/ILD)
- Acute interstitial pneumonia (AIP)
- Lymphoid interstitial pneumonia (LIP)
- Cryptogenic organising pneumonia (COP)

**Environmental and occupational diseases**

- Pneumoconiosis eg asbestosis, silicosis
- Extrinsic allergic alveolitis (EAA), for example, Hypersensitivity pneumonitis (bird fancier's lung).

**Multisystem diseases**

- Connective tissue diseases, for example, systemic sclerosis,
- Sarcoidosis
- Wegener's granulomatosis
- Tuberose sclerosis (lymphangioleiomyomatosis)
- Drug reactions, for example, amiodarone, methotrexate, bleomycin

**Rare lung diseases**

The common site of complications for systemic connective tissue disease (CTD) is the lung and this may manifest as ILD and/or pulmonary hypertension (PHT) among other presentations. There are several types of CTD associated with ILD and these include systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis, dermatomyositis, Sjogren's syndrome and mixed connective tissue disease (MCTD).

The prognosis and treatment of CTD-ILD may differ tremendously and this depends on the type of CTD such as SSc and the form of ILD such as idiopathic pulmonary fibrosis (IPF).

Pulmonary hypertension may present concurrently with ILD (PHT-ILD) or only present as a vasculopathy with no lung parenchymal involvement. [4]

*Pathogenesis of ILD:*

There are many types of cells that are involved in the pathogenesis of lung injury. Fibrosis may develop as a result of the insult to the lungs (Figure 1). Architectural disruption is produced when the cells in endothelial, epithelial, and interstitial compartments, together with the constituents of the innate and adaptive immune system interact with the extracellular matrix. This may result in inflammation and fibrosis and in the early stages both processes may co-exist. [5]

"*A plausible model of pathogenesis for parenchymal lung involvement in connective tissue disease includes initial alveolar epithelial injury triggered by environmental pathogens or inflammation*." [5] The repair pathways are initiated once there is damage of lung tissue and thereby the fibroblasts and myofibroblasts are released. The circulating cellular components and mediators including platelets and progenitor cells are recruited once the alveolar epithelial and endothelial compartments interact. It is interesting to know that the myofibroblasts are critical profibrotic cells that persevere in the affected lung tissue and this may determine the pattern and the type of fibrotic reaction that may occur (Figure 2). The extracellular matrix components, the matricellular proteins such as microfibrils and integrins and the soluble factors such as connective tissue growth factor (CTGF) all interact. The extent of destruction may be irreversible and the disruption of the architecture most likely determines the progression or reversibility of the lung disease.[5]

**Figure 1: Cellular pathogenesis of fibrotic lung injury.**

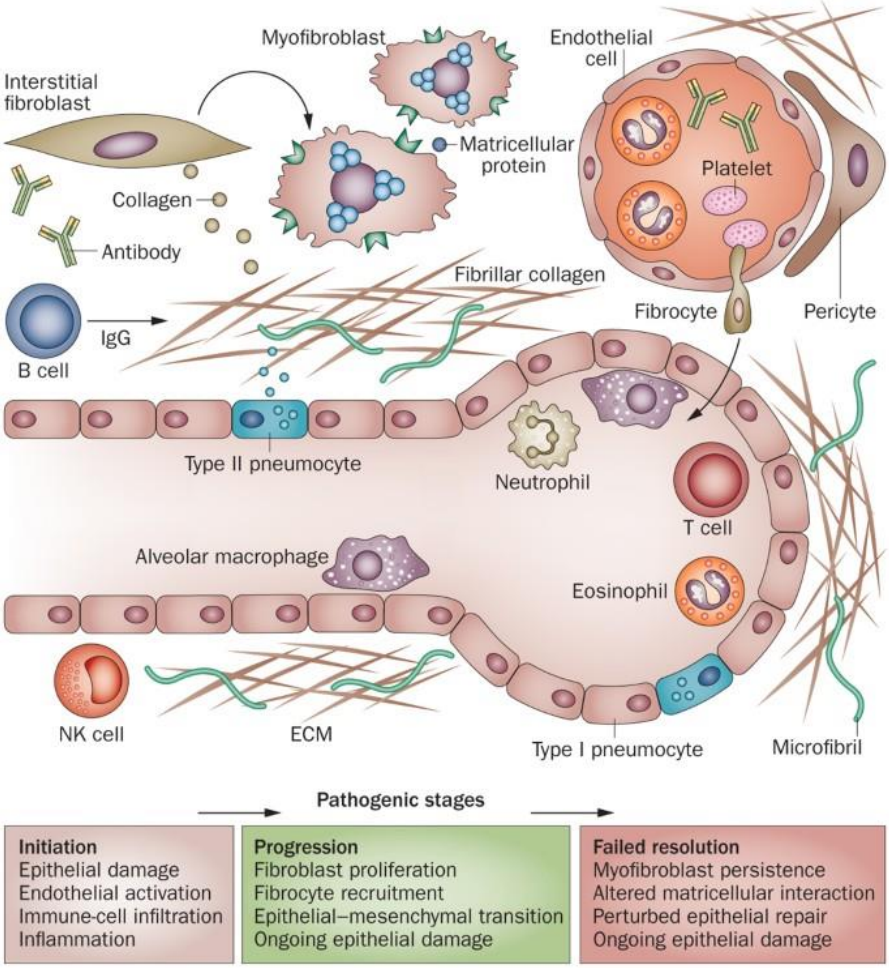


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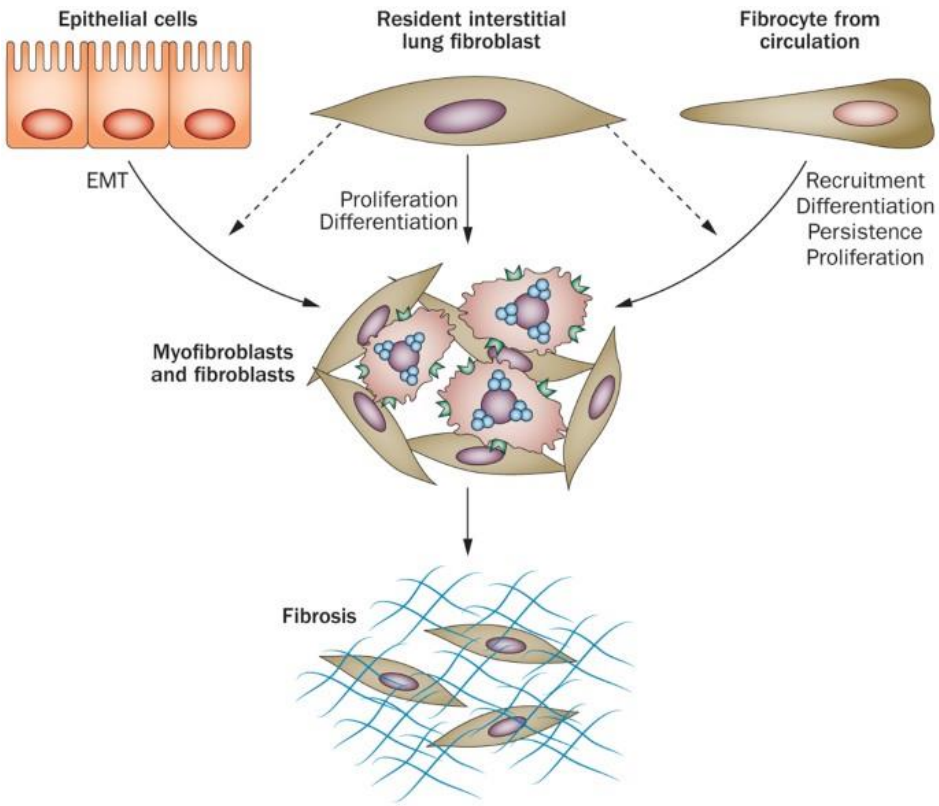
**Figure 2: Generation of profibrotic myofibroblasts after lung injury**

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### 1.2.2 Connective tissue associated lung disease

It is estimated that about one-third of patients with ILD have associated CTD. [6] CTD is a multifactorial disease that is associated with a heterogenous group of immunologically mediated disorders. This disease begins with an inflammatory process that usually results in abnormal repair and tissue damage. This leads to degeneration of the target organ with fibrosis and eventually loss of function.[7]

The most common disorders include systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis/polymyositis and Sjogren's syndrome. [4]

The lung is filled with connective tissue and a rich blood supply. This may be the explanation for it being a frequent target of autoimmune mediated injury in CTD.[7] A notable proportion of patients with CTD-ILD have progressive lung disease and this may lead to decreased physical function, poor quality of life and eventually death.[1]

#### *1.2.2.1 Systemic sclerosis*

Carlo Curzio was the first to identify a case of "scleroderma" in 1753. However, the word was first used in 1836 by Fantonetti. In 1862, Maurice Raynaud noted the triphasic vasospastic changes and in 1894 the systemic involvement of pulmonary and/or renal systems was described. There has been significant evolvement in the comprehension of the pathophysiology of scleroderma since it was first described 238 years ago. This however, did not make a

difference to the morbidity and mortality despite a few treatment options. Scleroderma remains the top cause of mortality from all CTD. [8]

In systemic sclerosis, unknown triggers activate the immune system. This manifests as specific autoantibodies such as anti-centromere (CENP), anti-topoisomerase I (topo I) also called scl-70 and anti-RNA polymerase III (RNAP). Once the fibroblast function is disturbed in patients with Ssc, it forms the typical skin thickening and fibrosis of visceral organs.[9]

SSc may present as either limited cutaneous SSc or diffuse cutaneous SSc. The limited form, otherwise referred to as "morphea" is usually mild and is limited to skin only. The diffuse form manifests with extensive skin thickening and severe internal organ involvement. [7] [10]This is a rare disease with a prevalence of 7-489/million and an incident rate of 0,6 to 122/million/year. [11] SSc affects adults of all ages, majority being women with a peak onset between 40 to 50 years.[7] [12]The estimated incidence of ILD in patients with SSc ranges between 25 to 90%. This range largely depends on the method used to diagnose ILD. Seventy percent of these patients are given a 10 year survival rate.[13] A study done over a 30 year period by VD Steen and TA Medsagar, demonstrated that the lung is the primary cause of deaths in patients with scleroderma and this manifests as pulmonary hypertension and pulmonary fibrosis.[12]

The most recent criteria for SSc was formulated by the American College of Rheumatism (ACR) and European League Against Rheumatism (EULAR) in 2013. This was a significant advancement in the diagnosis of SSc. It was formulated using the previous criteria by assimilating crucial elements such as proximal sclerodactyly, Raynaud's phenomenon, digital calcinosis, pulmonary fibrosis and specific autoantibodies to scleroderma. Emphasis was placed on the vasculopathic manifestations, which included puffy fingers. Clinical utilization of these criteria has markedly improved the sensitivity and specificity of this disease, particularly among patients who present with early, mild or limited disease.[14, 15]

#### *1.2.2.2 Systemic lupus erythematosus*

Systemic lupus erythematosus is an autoimmune disease in which autoantibodies (AA) such as double and single stranded DNA, histones and extractable nuclear antigens (ENAs) are targeted against the intracellular antigens of the cell nucleus. [16] SLE affects 15-124 per 100,000 of the world's population. The female:male ratio is 6:1 and occurs mainly in women of childbearing age. In 3-18% of the cases, it may present late between the ages of 50-65. These patients may present with an extensive range of symptoms. The common symptoms at presentation may be fever, lymphadenopathy, fatigue, arthralgia and weight loss. Patients may eventually develop serositis, sicca syndrome, Raynaud's phenomenon, neuropsychiatric symptoms and lung disease. [7]

The diagnosis of SLE is based on the ACR criteria. Lupus is diagnosed when at least 4 out of the 11 criteria are met.[17] (Table 3)

**Table 3: 11 Criteria for diagnosing SLE (ACR guidelines)**

| No | Clinical Signs |
|---|---|
| 1 | Malar rash |
| 2 | Skin rash |
| 3 | Photosensitivity |
| 4 | Mouth or nose ulcers |
| 5 | Non erosive arthritis |
| 6 | Cardio-pulmonary involvement |
| 7 | Neurological disorder |
| 8 | Renal disorder |
| 9 | Haematological disorder |
| 10 | Immunological disorder |
| 11 | Positive ANA |

There is a vast range of laboratory abnormalities found in patients with SLE. [7] However, the diagnostic and classification criteria for SLE is dependent on the autoantibodies (AA) and the antinuclear antibody (ANA). [7] Most autoantibodies are not specific for SLE and since they are polyclonal, they are often directed against multiple targets.[16]

Although there are more than 200 various AA, less than 20 are considered significant.[18] The following are the most common laboratory tests used for the diagnosis of SLE - antinuclear antibodies (ANA), anti-DNA antibodies (ssDNA and dsDNA), antihistone antibodies, extractable nuclear antigen (ENA) – anti-Ro and anti-La, antibodies to anti-smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), anti-ribosomal antibodies, anticardiolipin antibodies (ACA), acute phase reactants (eg.erythrocyte sedimentation rate (ESR),CRP),cytokines (eg. Soluble interleukin 2 receptor or tumour necrosis factor (TNF), complement, anti-C1q antibodies, anti-endothelial cell antibodies, anti-neutrophil cytoplasmic antibodies. [16] The most popular diagnostic tests are ANA, anti-dsDNA and anti-Smith. [7] ANA positive results should undergo more specific assays as the clinical importance cannot be determined from the titre or pattern. However, it is more relevant when there are higher titres (>1/160).[16]

The treatment of choice for SLE is hydroxychloroquine. The drug is known to assist with reducing the constitutional symptoms and disease flares. Depending on the organs affected, the use of glucocorticoids and cytotoxic agents (eg. azathioprine, cyclophosphamide and methotrexate) may be considered. [17]

#### *1.2.2.3 Mixed connective tissue disease*

Due to the lack of diagnostic criteria there is limited epidemiological data available. However, MCTD has a prevalence of approximately 4 per 100,000 and occurs predominately in females around the age of 35. It is a systemic autoimmune disorder that is characterised by various overlapping features and these include SSc, SLE, PM/DM and RA. The presentation type varies. Positive antibodies against U1 small nuclear ribonucleoprotein autoantigens may be present in their serology. [7]

#### *1.2.2.4 Undifferentiated connective tissue disease(UCTD)*

UCTD refers to patients who do not fulfil the diagnostic criteria for any of the CTD's but these patients inherently exhibit signs, symptoms and serological incongruency that is indicative of an autoimmune disorder. UCTD occurs mainly in females between the ages of 30 to 50. In 20-40% of cases they may evolve into a CTD that fulfils a diagnostic criteria.[7] The term UCTD was re-evaluated and in 2015, the European Respiratory Society (ERS) and American Thoracic

Society (ATS) formulated the term IPAF (Interstitial Pneumonia with Autoimmune features) if the patient has interstitial lung disease clinically and radiologically.[19, 20] IPAF is now emerging as the leading cause of CTD-ILD. [21]

**Table 4: Major causes of death and predictors of worse outcome in connective tissue diseases.**

| | **Major causes of death** | | |
|---|---|---|---|
| **Disease** | **Direct or indirect disease complications**[#] | **Comorbidities** | **Predictors of worse outcome** |
| **RA** | Infection (mainly pneumonia)<br>**Pulmonary fibrosis**<br>Osteoporosis/fractures<br>Cancer | Cardiovascular disease (*e.g.*, ischaemic heart disease, atrial fibrillation and heart failure) Cerebrovascular disease | Male sex<br>Older age<br>Worse physical disability<br>Extra-articular manifestations<br>Positive rheumatoid factor<br>**Pulmonary fibrosis**<br>Corticosteroid use<br>Comorbidities |
| **SSc** | **Pulmonary hypertension**<br>**Pulmonary fibrosis**<br>Scleroderma renal crisis<br>Cancer | Liver disease<br>Inflammatory bowel disease<br>Multiple sclerosis<br>Neuropsychiatric disorders | Older age at onset<br>Male sex<br>Diffuse skin involvement<br>Scleroderma renal crisis<br>**Pulmonary fibrosis**<br>**Pulmonary hypertension**<br>Anti-topoisomerase 1 (Scl-70) and anti-U1 RNP antibodies |
| **SS** | Lymphoproliferative disorders | Cardiovascular, endocrine, gastrointestinal and psychological disorders | Low C3 and/or C4 levels at the time of diagnosis |
| **SLE** | Infection<br>Renal and cardiovascular disease<br>Haematological manifestations<br>Cancer<br>Osteoporosis/fractures | Cardiovascular and cerebrovascular disease (*e.g.* hypertension, atherosclerosis and thromboembolic events) | Female sex<br>Disease duration <1 year<br>Disease onset after the age of 50 years<br>Older age<br>Black/African-American race<br>Haematological manifestations<br>Active disease<br>Immunosuppressive therapy |

| Disease | Major causes of death | | Predictors of worse outcome |
|---|---|---|---|
| | **Direct or indirect disease complications**[#] | **Comorbidities** | |
| **PM/DM** | Aspiration pneumonia<br>Cancer (particularly in DM) | Cardiovascular disease (*e.g.* hypertensions and ischaemic heart disease)<br>Venous thromboembolism<br>Diabetes | Female sex<br>Older age at onset<br>Shorter disease history<br>Failure to induce remission<br>Smoking<br>Dysphagia |
| **MCTD** | **Pulmonary hypertension**<br>**Pulmonary fibrosis**<br>Scleroderma renal crisis<br>Infection | Cardiovascular and thromboembolic events | **Pulmonary hypertension**<br>Evolution into SLE or SSc |
| **AS** | Musculoskeletal abnormalities (spinal fractures and cervical subluxation)<br>Secondary amyloidosis<br>Infection | Cardiovascular and cerebrovascular disease<br>Bowel, liver and haematological disease<br>Psychiatric disorders | Permanent pain<br>Ongoing disease activity<br>Disease manifestations in hips, peripheral joints, entheses, uvea and heart<br>Limitation of spinal mobility<br>Osteoporosis<br>Development of amyloidosis |

- RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis; RNP: ribonucleoprotein. [#]: complications and comorbidities may be difficult to distinguish; therefore, this separation is somewhat artificial and should be viewed as such.

[7]



### 1.2.3 Clinical presentation

Patients with CTD present with a vast array of symptoms depending on the nature and severity of their connective tissue disease. The most common presentation for CTD-ILD is progressive dyspnoea and cough. [3] Cough and wheezes are usually "airway centred". A dry cough is usually associated with UIP/IPF and a productive cough manifests when there is excessive secretions within the tracheobronchial tree with advanced ILD. This occurs when patients develop traction bronchiectasis or chronic bronchitis. There may be haemoptysis in pulmonary haemorrhagic diseases such as granulomatosis with polyangiitis (GPA) formally known as Wegener's granulomatosis or Good pasture's syndrome. Haemoptysis in patients with UIP/IPF may lead the physician to be concerned about complications such as pneumonia, lung malignancy and pulmonary embolus. Patients who have RA, SLE or drug induced lung disease may present with pleurisy. [22]

Patients with ILD usually present with bilateral crackles on examination.[3] Dyspnoea caused by exertion needs to be further investigated as this may result from other causes such as anaemia, extrapulmonary conditions, cardiac involvement, musculoskeletal limitation and deconditioning. [5]

The NYHA (New York Heart Association) is a subjective classification that is easily applied in routine clinical practice. (Table 5) It performs better in patients who present with NYHA 111/1V and less so in patients with NYHA 1/11.[23] Although originally meant for heart failure it can be used in patients with chronic parenchymal lung disease for clinical assessment. It is a useful tool.

**Table 5: NYHA classification**

| CLASS | LEVEL OF CLINICAL IMPAIRMENT |
|---|---|
| 1 | No limitation of physical activity |
| 11 | Slight limitation of physical activity, in which ordinary physical activity leads to fatigue, palpitation, or dyspnoea; the person is comfortable at rest |
| 111 | Marked limitation of physical activity, in which less-than-ordinary activity results in fatigue, palpitation, or dyspnoea; the person is comfortable at rest |
| 1V | Inability to carry on any physical activity without discomfort but also symptoms of heart failure at rest, with increased discomfort if any physical activity is undertaken |

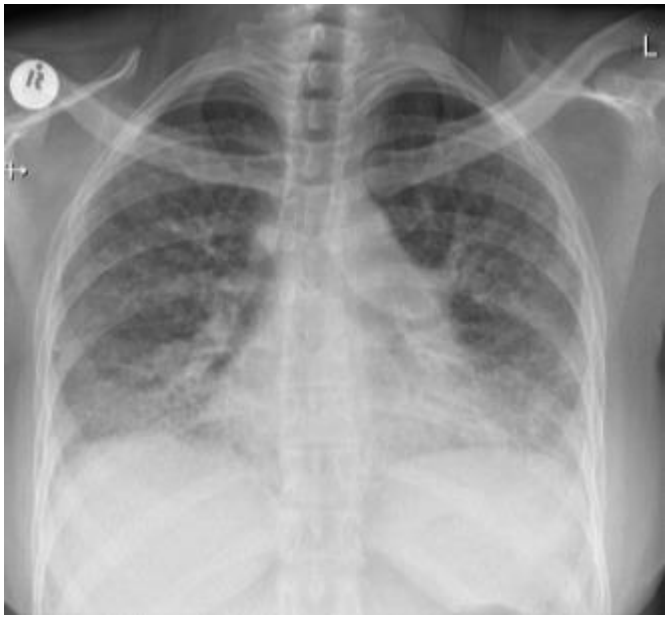
### 1.2.4 Investigation of ILD

Even though the traditional means of identifying CTD-ILD are clinical and via chest radiography, the hallmark for identifying CTD-ILD is by HRCT. [5]

#### *1.2.4.1 Chest radiograph*

The chest radiograph may be abnormal in patients with significant respiratory symptoms. According to previous data, 10% of cases confirmed by lung biopsy had a normal chest radiograph. [22] Chest radiography may demonstrate diffuse infiltrates.[3] Chest radiography may be of value for monitoring of patients with ILD. There are not enough data to support its use for diagnostic purposes.[22]

**Figure 3: Chest radiograph of a patient with ILD**




*** Permission obtained from BREC, DOH and hospital (IALCH).

#### *1.2.4.2 Spirometry*

Spirometry is used in ILD to assess disease severity, and to monitor progression and response to therapy. It is important to have a stepwise approach to achieve a reliable interpretation.[24] The breadth of the normal range of an adult patient is 80-120% of predicted. In ILD typically a restrictive defect is present. This is evidenced by a decreased forced vital capacity (FVC) and total lung capacity (TLC) and an increased FEV1: FVC > 0,8. There may be reduced diffusion of carbon monoxide (DLCO) and poor lung compliance.[5] In other words, lung function tests reveal reduced lung volumes, impaired gas transfer and hypoxaemia.[3]

*Forced vital capacity*

The definition of a reduced FVC is a value that is below the 5$^{th}$ percentile in adults or less than 80% of predicted in children under 18 years old. To identify restrictive defects, obstructive defects and mixed patterns, the FVC and FEV1/FVC ratio is used.[24]

*Six minute walk test*

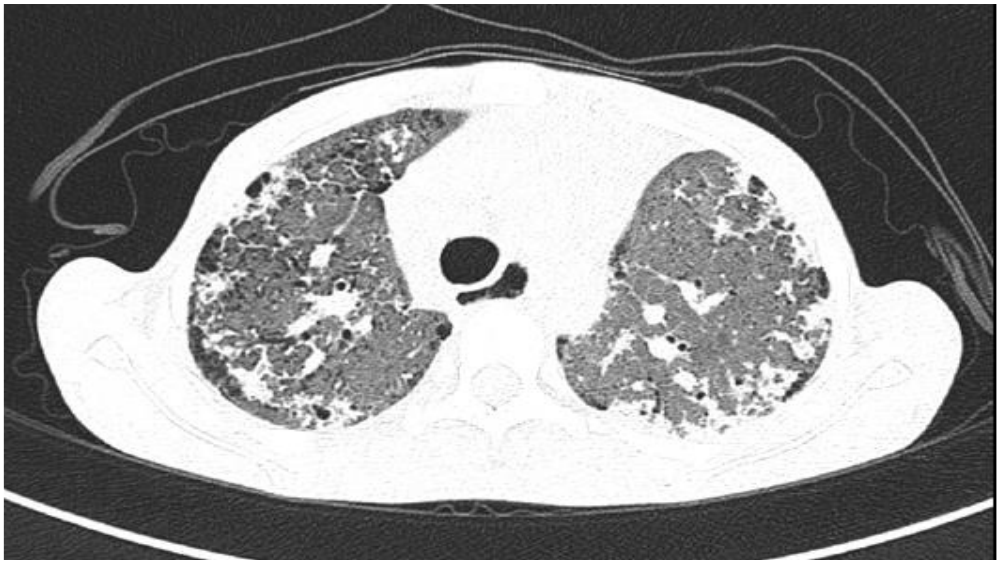
The 6MWT is a safe, low complexity test in which the patient walks along a flat, hard surface with no obstruction in a 30 metre corridor for a period of 6 minutes. The outcome is measured in metres and the level of dyspnoea and fatigue are secondary variables which are measured using a standardised Borg scale. [25] It may be beneficial to test the arterial oxygen saturation before and after the 6MWT using a reliable pulse oximeter. However, this is not mandatory. Healthy subjects are able to walk a distance ranging from 400m to 700m. [26, 27] A previous study demonstrated the median 6MWD to be approximately 580m for 117 healthy male subjects and 500m for 173 healthy female subjects. In another study of 51 healthy older subjects the mean 6MWD was 630m.[25]. In patients with moderate to severe pulmonary disease this test objectively assesses the functional exercise capacity, before and after treatment comparisons and to predict hospitalisation and death. The change in 6MWT may predict morbidity and mortality and is useful in treatment decisions and clinical trials.[26, 27]

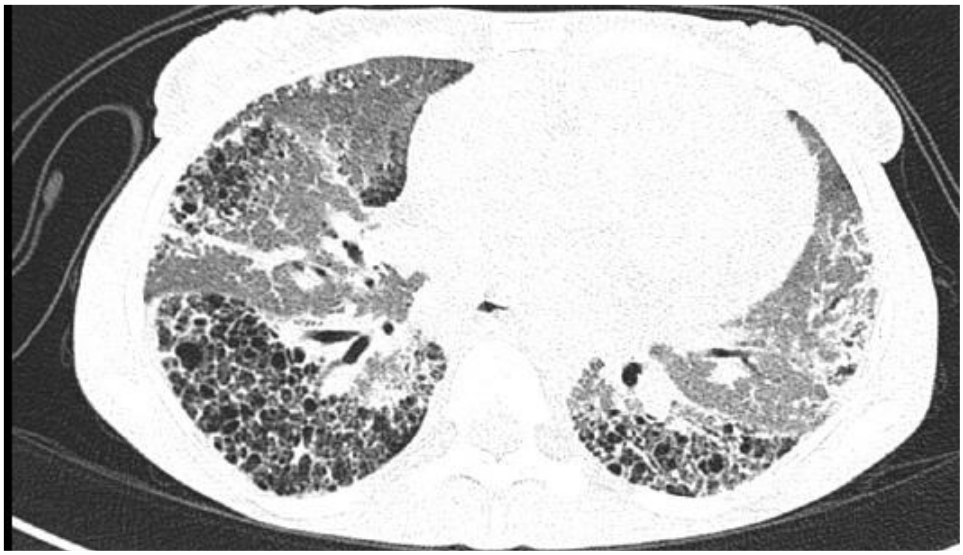
A study of 102 healthy Caucasian adults, between the ages of 20 to 50 years, demonstrated a mean 6MWD of 614m, ranging from 459 to 738m. [28] The inclusion and exclusion criteria from six articles were analysed and this included subjects who had a broad spectrum of pulmonary diseases. The mean 6MWD ranged from 295 to 551m at baseline and a change of 14 to 30,5m was found to be significant. [29]

#### 1.2.4.3 *High resolution computed tomography*

HRCT scan is the gold standard for diagnosing ILD. It is both sensitive and specific in identifying the type of ILD. However, due to this test being sensitive it may not be a good screening tool as it may portray subclinical abnormalities that do not necessarily progress to significant lung disease. Therefore this test should be used according to existing protocols to confirm or exclude CTD-ILD in the higher risk groups or the groups in which clinical, chest radiograph and abnormal lung spirometry suggests ILD.[5] The radiological pattern visualised on HRCT scans most often suggests the underlying histological pattern. For example, a usual interstitial pneumonia (UIP) is characterised by the presence of honeycombing and reticular infiltrates. There should be an absence of various features such as diffuse mosaic attenuation, air trapping, consolidation, micronodules and extensive ground-glass opacification. [30] (Figure 4,5)

**Figure 4 and 5: HRCT scan of a patient with UIP**





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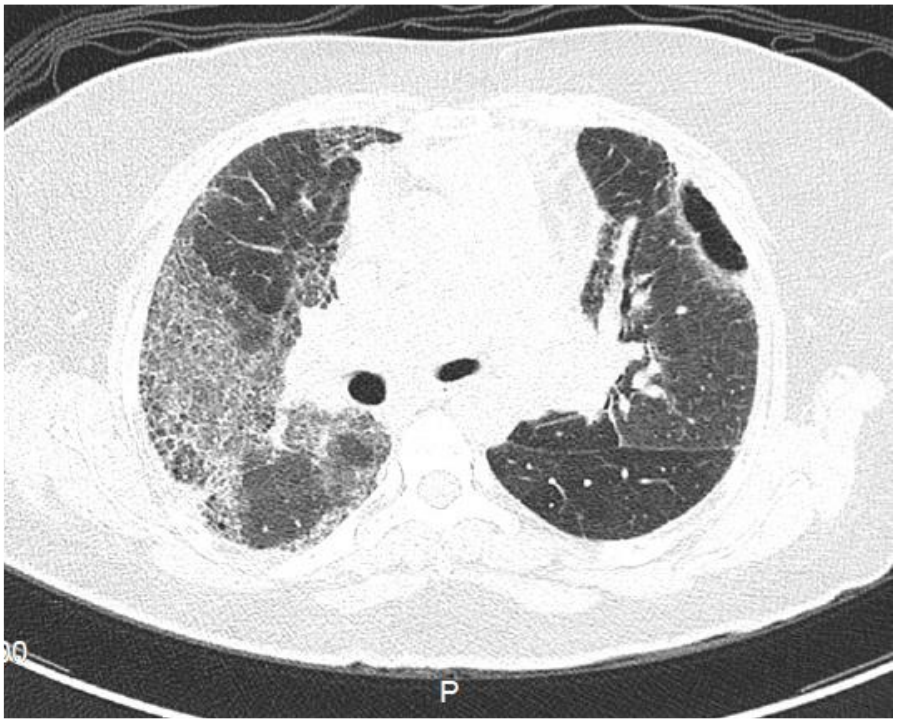
It may be difficult to distinguish between UIP and nonspecific interstitial pneumonia (NSIP) patterns on HRCT scan as a significant proportion of the scans that portray a NSIP pattern will inadvertently have a UIP histologic pattern and more importantly, NSIP pattern, over time, may evolve to a UIP pattern.[30] (Figure 6)

**Figure 6: HRCT scan of a patient with NSIP**




*** Permission granted by BREC, DOH and hospital (IALCH).

### 1.2.5 Lung biopsy in CTD-ILD

Despite HRCT scan being the gold standard for diagnosing patients with CTD-ILD, there is the option to perform a surgical lung biopsy (SLB) especially in those with diagnostic uncertainty. Surgical lung biopsies may confirm the type of ILD. The presence of a UIP pattern on HRCT scan frequently predicts the presence of UIP histopathologic pattern on SLB with a high degree of specificity. Patients with suspected ILD who require histologic confirmation may have it done by way of either one of two methods: VATS (video-assisted thoracoscopy) or open lung biopsy. This enables the clinician to achieve a confident diagnosis in cases where there are diagnostic uncertainties [22, 30]. A number of studies have shown that the pattern seen on HRCT scan taken together with the clinical findings can predict the histopathological findings. A SLB will not benefit the patient with regards diagnosis, treatment or prognosis. Patients with no underlying CTD, UIP pattern on HRCT scan and over the age of 65 years and no clinical or radiological evidence to suggest an alternative diagnosis can be confidently diagnosed as having IPF. There is therefore no indication for a SLB in these patients. However, a SLB may be indicated in those subjects who have atypical imaging features for the underlying CTD or an unusual clinical course.

Mortality after a SLB is relatively high in patients with severe disease and significant comorbidities. The most common complications following a SLB include a pneumothorax, haemothorax, and acute exacerbation of IPF or other ILDs. Some of the patients may require ICU admission because of the complication. A multidisciplinary discussion (MDD) is recommended before undertaking a SLB. Patients must be counselled regarding the procedure and complications.[30-32]

### 1.2.6 Immunosuppressive treatment in CTD-ILD

The specific types of ILD are important to determine the choice of drug as well as prognosis. Not all CTD-ILD requires treatment as some patients do not progress and the risk/benefit ratio needs to be considered. There are currently robust prospective trials that may assist with future treatment decisions once completed. Thus far, the treatment for most CTD-ILD is based on retrospective studies or small prospective studies. [33]

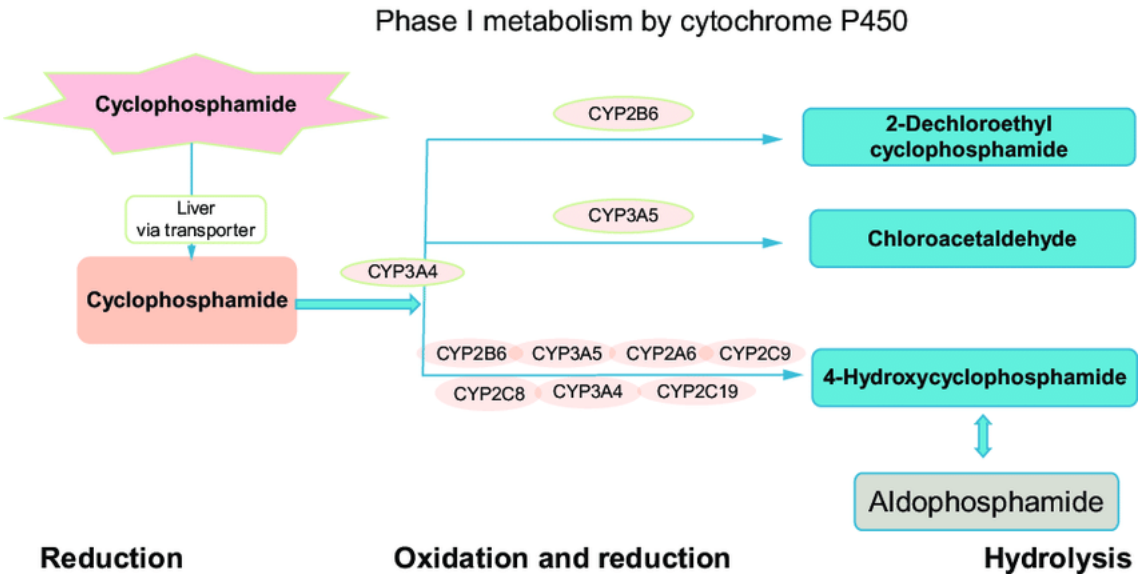
The most common used immunomodulatory drugs used in the management of CTD-ILD are prednisone, mycophenolate mofetil, azathioprine, cyclophosphamide and rituximab. [31] Even though there are controversies in treatment approaches, cyclophosphamide is the drug that is generally accepted as treatment of choice for patients with severe or progressive SSc-ILD and other connective tissue associated ILD's that have failed initial treatment.[34][35] Mycophenolate mofetil, azathioprine with low dose prednisone are commonly used as first line treatment for the majority of the CTD-ILD's.[36]

#### *1.2.6.1 Cyclophosphamide*

CYC belongs to a group of oxazaphosporines and is a highly potent immunosuppressive and immunomodulatory agent that has shown efficacy in inducing and maintaining remission in autoimmune diseases. CYC is an alkylating agent prodrug. It has to pass through a complicated process of metabolic activation and inactivation. The efficacy and toxicity of CYC treatment is not well understood in relation to its metabolites. Some studies have suggested ways of optimising CYC treatment. This is because of the variations in the balance of activation and inactivation of the metabolites. Individual differences, auto-induction and drug-drug interactions may necessitate dose escalation in some patients.[37] [38]

The pharmacokinetics of CYC cannot be predicted using the parent compound. The activity resides in the metabolites. In order for CYC to become active, it needs to undergo hepatic transformation to form 4-hydroxycyclophosphamide, which eventually breaks down to form aldophosphamide, commonly referred to as phosphoramide mustard. The dose of CYC varies from 1,5 to 60mg/kg/day. The drug has a steep dose-response curve which may lead to unfavourable outcomes if the dose is reduced. [39, 40] (Figure 7)

**Figure 7: Metabolism of cyclophosphamide**

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CYC treatment may cause nausea, bone marrow suppression, haemorrhagic cystitis, carcinoma of the bladder, increased risk of opportunistic infections and haematological cancer.[1] There have been multiple observational and randomised controlled trials of SSc-ILD and CYC. The drug remains the treatment of choice. The Scleroderma Lung study 1 has provided the most substantial evidence supporting CYC. This was a multi-centre double-blinded RCT that involved 158 patients with SSc-ILD. These patients were treated with oral CYC for one year and showed symptomatic improvement. However, the improvements regressed after two years. Hoyles *et al* conducted a RCT which involved CYC administered monthly intravenously for 6 months with Prednisone and Azathioprine. This showed an improvement in the FVC but this did not reach statistical significance.[36]

In a study by Tashkin 2006, 158 participants with SSc-ILD were enrolled. Seventy-nine patients were in the CYC group. Twenty of the participants withdrew within one year and this was due to the adverse effects of the drug. After one year, there was an overall improvement in quality of life, improvement in FVC and skin tightening. FVC showed no decline after 24 months. [41] In Hoyles 2006, only 2 participants withdrew from a group of 22 participants and this withdrawal was also attributed to adverse effects. [42]

A meta-analysis encompassing four trials with a total of 495 participants was conducted. One trial involved daily oral CYC or intravenous CYC every 4 to 6 weeks for 6 months. Tashkin 2016 studied participants who were administered CYC for 12 months and mycophenolate for 24 months. Zhang 2015 used both mycophenolate and CYC for a duration of 12 months. Overall, these four trials revealed no significant difference in FVC percentage predicted at 12 months. Overall, the evidence was considered to be of low quality. More studies are required perhaps with smaller numbers.[1, 43, 44]

#### *1.2.6.2 Corticosteroids in CTD-ILD*

The use of oral corticosteroids in CTD-ILD has been in practice for decades. While corticosteroids are indicated in most subtypes of ILD's, the practice remains controversial. This is due to the multiple side effects associated with corticosteroid use. The efficacy of corticosteroids is questionable in some subtypes of ILDs. Some trials have proven that a combination of corticosteroids and immunosuppressive drugs are more effective rather than corticosteroids alone. Corticosteroids are therefore administered in the induction therapy in most patients. [45] There should be careful monitoring of corticosteroids in patients with SSc due to the complication of scleroderma renal crisis. Low doses of corticosteroids are prescribed in these patients. [46] Previously, corticosteroids were widely for ILDs with a UIP pattern or fibrotic NSIP. However, recent studies confirm that there is poor evidence base for the use of corticosteroids. In this group of patients steroids are used when the patient has an acute exacerbation.[47]

#### *1.2.6.3 Antifibrotic drugs*

There are currently only two anti-fibrotic drugs registered for the use of fibrotic lung disease. Previous phase III trials have demonstrated that pirfenidone and nintedanib reduce the rate of decline of the FVC in patients with mild to moderate IPF and SSc-ILD. This translates to an improvement in the quality of life. The most recent phase III trials have demonstrated that nintedanib retards the progression of ILD in a broad spectrum of fibrosing ILDs, including CTD-ILD with a progressive phenotype. [48] According to a study, pirfenidone is the preferred antifibrotic drug shown to reduce the rate of progression of FVC. Its side effects profile is tolerable and results in a general improvement in quality of life for patients with mild to moderate IPF. Studies that are more robust are required. [49]

There were 576 participants who enrolled in the safety and efficacy of nintedanib in systemic sclerosis trial (SENCIS trial). This was a randomised, double blind, placebo-controlled trial in which mycophenolate mofetil was used at baseline for most patients for at least 52 weeks. This study demonstrated that the combination of mycophenolate mofetil and nintedanib reduced the rate of decline of FVC in these participants and offered a safe treatment option for patients with SSc-ILD. However, more data is required to be certain this finding. [50]

### 1.2.7 Complications of CTD-ILD

#### *1.2.7.1 Pulmonary hypertension*

There is a high prevalence of pulmonary hypertension estimated between 30-40% in patients with ILD. This results in progressive dyspnoea associated with exercise limitation, reduced DLCO on PFT or oxygen desaturation on 6MWT. Clinical suspicion arises when symptoms seem disproportionate to the extent of parenchymal lung disease. PHT is ultimately associated with a poor prognosis. Patients with PHT are usually diagnosed late in the disease due to the clinical symptoms being non-specific. There are helpful investigations that may assist the clinician in diagnosing PHT, however right heart catheterisation remains the confirmatory diagnostic tool. [51] [22] Transthoracic echocardiography is an acceptable screening investigation especially when right heart catheterisation is not easily available. [22] Patients may require long term oxygen especially for those who have advanced ILD, chronic hypoxia (<8kPa) or cor-pulmonale [22]. Currently, the use of phosphodiesterase V inhibitors such as sildenafil or tadalafil may be used to prevent progression of disease. These drugs are restricted to certain facilities and patients must meet the appropriate criteria for their use in CTD-ILD. [22]

#### *1.2.7.2 Pulmonary fibrosis*

Pulmonary fibrosis in ILD is characterised by a progressive decline in lung function, which may lead to respiratory failure and eventually death. Typically, in ILD the common subtypes associated with pulmonary fibrosis are a UIP pattern and fibrotic NSIP. Currently there is no cure for this disease and ongoing studies are crucial in the comprehension of this untreatable disease. [52] There may be a role for antifibrotics such as pirfenidone and nintedanib. [53]

### 1.2.8 The impact of Covid-19 pandemic in ILD particularly fibrotic ILD

The current global pandemic, Covid 19, has altered the ways we manage patients. There have been massive disruptions in the work up, diagnosis and treatment of patients with CTD-ILD. There is reduction in healthcare utilization due to fear of contracting Covid 19. Fear of exposing health care workers to aerosol-generating procedures compounds the delays in investigations. The average delay in diagnosing ILD, from symptom onset ranges from one year onwards depending on the health care facilities available. During the covid-19 pandemic, this has caused reduced access to the relevant diagnostic tests and delay in specialised care. This is due to reduced access to clinics, pulmonary function testing, bronchoscopies and SLB. Bronchoscopies and PFT's are avoided in symptomatically stable patients, as they are a high risk to both patients and health care workers. In addition, Long Covid can present as ILD. Robust data is required on how to manage CTD-ILD in the setting of a covid-19 pandemic.[31]

# CHAPTER TWO: AIMS AND OBJECTIVES

## 2.1 Aim of study

The aim of this study was to determine the clinical, radiological and pulmonary function responses of patients with CTD associated ILD who received CYC in our local setting.

## 2.2 Specific Objectives:

2.2.1 Objective 1:

To determine the number of patients that received Cyclophosphamide in the management of connective tissue associated lung disease.

2.2.2 Objective 2:

To describe the demographic profile of the study participants.

2.2.3 Objective 3:

To examine the specific patterns of interstitial lung disease on HRCT.

2.2.4 Objective 4:

To compare the HRCT Scan findings pre and post Cyclophosphamide treatment.

2.2.5 Objective 5:

To assess the functional status of patients pre and post CYC treatment by using the NYHA classification.

2.2.6 Objective 6:

Describe the pulmonary function test parameters before and after treatment.

2.2.8 Objective 7:

Describe the side effects encountered after the administration of CYC.

2.2.9 Objective 8:

Describe the outcome of disease for patients who completed 18 cycles of treatment compared to those that did not complete 18 cycles.

# CHAPTER THREE: GENERAL METHODOLOGY

## 3.1 Study Design

The study is a retrospective review.

## 3.2 Setting

This study was conducted in the Department of Pulmonology at Inkosi Albert Luthuli Central Hospital and involved both inpatient and outpatient data. This hospital is a quartenary institution and is the only government hospital in Kwa-Zulu Natal with specialist clinics for the management of patients with CTD-ILD.

Ethics approval was granted by the University of Kwa-Zulu Natal research ethics committee (BE344/19) and management of IALCH, Durban.

## 3.3 Participant Selection and Sampling strategy

The study population consisted of all adults over the age of 18 years old diagnosed with CTD-ILD and treated with CYC at Inkosi Albert Luthuli Central Hospital. The data obtained was over a ten year period from January 2009 to December 2018 and identified using the Data Warehouse software package (see below).

There have been 3 electronic hospital information systems at IALCH (MEDICOM -2002 to May 2011, SOARIAN -May 2011 to August 2016 and MEDITECH August 2016 to date). Not all data was migrated from one system to another.

The data recorded on all these systems were extracted, transformed and loaded into the central Oracle data warehouse where data is integrated to form one seamless view of all the recorded data (historical and current hospital information systems).

The data warehouse is used for reporting and data analysis and is the core component of business intelligence. This data is used to populate the Qlik Sense business intelligence tool with standard dashboards required for Hospital Reporting and Key Performance Indicators.

Due to the complexities of data required for research projects, the Qlik Sense standardised dashboards are not often used for this purpose. Customized extraction queries are written to extract the core data required for the researcher from the central Oracle data warehouse. We used the core data received to continue this research (e.g. MEDICOM, SOARIAN and/or MEDITECH, sometimes Qlik Sense).

Patients were identified on the electronic chart database with the unique hospital numbers.

We used the patient chart numbers to access each patient's records. The charts of all patients evaluated was collected and analysed using the inclusion and exclusion criteria and this data was recorded on Microsoft Excel.

CTD-ILD is not a common condition. The sample size of 62 was considered to be adequate when compared with similar studies in the literature.

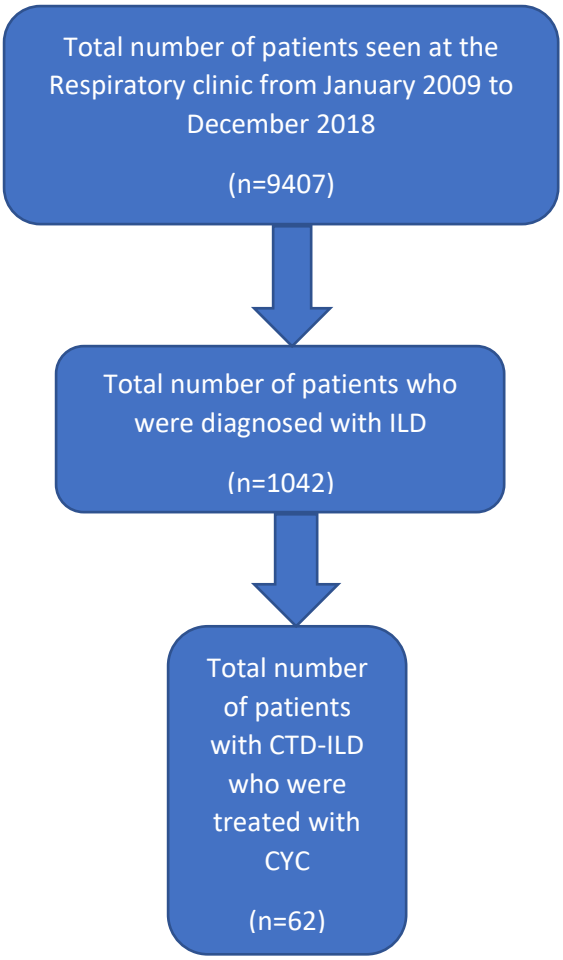
### *3.3.1 Inclusion Criteria*

All adult patients (>18 years) who were diagnosed with CTD associated ILD and treated with CYC in the department of pulmonology at IALCH between the period January 2009 to December 2018.

### *3.3.2 Exclusion Criteria*

We excluded all patients who were treated before January 2009 and after December 2018. (Figure 8). Patients who did not meet the international criteria for the diagnosis of CTD-ILD and patients who had incomplete data on admission and follow up visits were also excluded. There was a total number of 9407 patients seen in the respiratory department during this period. 1042 were diagnosed with ILD and only 62 patients met the inclusion criteria for our study.

**Figure 8: Stepwise approach of patient selection for study group**




### *3.3.3 Data Collection*

Demographic data, underlying connective tissue disease, pulmonary function tests, radiological images, co-morbid conditions as well as cyclophosphamide schedule and dosing was collated.

*Variables:*

1. Age
2. Race
3. Gender
4. CTD type
5. Number of doses completed
6. Inflammatory markers (WCC, ESR and CRP)
7. Clinical presentation including NYHA classification
8. Radiological findings including High Resolution Computed Tomogram Scan (HRCT Scan)
9. Pulmonary Function Test – Spirometry (FVC), 6MWT
10. Side effects of CYC
11. Complications - PHT
12. Outcomes after treatment

The above was collated after accessing each patient's chart via their KZ number and capturing on Microsoft Excel. This data was submitted to the biostatistician for analysis. The comparison of those patients that completed treatment versus those that did not complete treatment for the particular group was documented and analysed. The patient's information was anonymized by means of a numbering system.

*3.3.3.1 Spirometry*

The pulmonary function laboratory at IALCH is a specialised department with an array of sophisticated and modern equipment managed by two experienced clinical technologists. The physician orders the tests electronically. A resuscitation trolley is fully equipped, checked regularly and easily available should the need arise.

The spirometry equipment is a Jaeger Master Screen unit by Cardinal Health. The equipment requires ongoing maintenance to ensure that it is functional at all times by checking the ambient conditions and volume calibration. This is critical in ensuring that the readings recorded by the spirometer are accurate.

In the pulmonary function laboratory at IALCH calibration is performed every morning before any tests are conducted, after a power failure and after pneumotachometers have been changed for cleaning purposes. Ambient conditions (such as temperature, humidity, barometric pressure and altitude) are recorded before performing calibration. These ambient values are obtainable from automatic sensors in the laboratory. A calibration syringe with a known volume of 3L is used to check the volume accuracy of the spirometer. A bacterial mouth filter is attached to the end of the 3L calibration syringe. The syringe connects to the spirometer. This is to ensure that the calibration is performed under the same conditions at which flow is measured and that the same amount of resistance is present. Air is pumped into the spirometer several times until calibration is successful.

Once calibration is successful and the machine is ready, the patient's height and weight, without shoes is checked and the age, race and sex is documented. The technician confirms that there are no contraindications before commencement of the test. If the patient is unable to stand in an upright position then one can obtain an estimate by measuring the arm span. The patient needs

to be sitting upright in a comfortable chair with arm rests, tight clothes need to be loosened and dentures may not be removed unless they are loose.

The patient sits in an upright position, feet flat on the floor. The mouth -piece is attached to the pneumotachometer. Instructions are given to the patient. The patient places his/her mouth around the mouthpiece with the lips sealed tightly and a nose clip on. The patient breathes normally (tidal breathing). The patient expires, hard, fast and sharp out for a minimum of 6 to 15 seconds until the plateau is reached. A deep inspiration is then taken. A flow volume loop is then obtained.

*3.3.3.2 6MWT*

The clinical technologist at baseline conducted the 6MWT. The test was repeated every 3 months of treatment and post treatment. Vitals, including oxygen saturation, were checked and documented prior to the test. Even though the guidelines mention a passage of 30m in length, we use a standardised passage of 50m. The test requires the following equipment: a reliable stopwatch, lap counter, cones and a flat, hard surface. The patient usually sits for a few minutes to rest prior to commencing the test. Cones are placed in the demarcated area and the patient begins to walk at their own comfortable pace. A Borg score is then measured and documented along with the total distance walked during the 6 minutes. (Table 6) Oxygen saturation is rechecked at the technician's discretion.

**Table 6: The Borg Dyspnoea Scale**

| | |
|---|---|
| 0 | Nothing at all |
| 1 | Just noticeable |
| 2 | Very slight |
| 3 | Slight |
| 4 | Slight-moderate |
| 5 | Moderate |
| 6 | Some difficulty |
| 7 | Moderately severe |
| 8 | Severe |
| 9 | Very severe |
| 10 | Maximum shortness of breath |

*Grading must be done pre and post-test using the patient's baseline dyspnoea and overall fatigue post-test.

*3.3.3.3 HRCT scan*

A baseline diagnostic HRCT scan of the chest was performed on all the patients. Some patients who required admission had their scans as inpatients. Some patients had elective bookings for the HRCT scans. A qualified radiologist employed at IALCH reported all the HRCT scans of the chest. This institution has state of the art HRCT scanners. The scanner used is the Siemen's flash sensor with a somatom definition flash. Thin sliced chest images are obtained in 0,5 to 1 seconds. Patients are examined supine and the scans are recorded when the patient takes a deep inspiration. The scanner utilised is able to obtain around 256 slices. The images are captured on the electronic system and hence are available for pulmonologists to review.

## 3.4 Ethical considerations

The necessary ethical approvals were obtained from the Kwa-Zulu Natal department of health as well as the University of Kwa-Zulu Natal BREC committee with BREC reference number (BE344/19). No consent was required from these patients as this is a retrospective study and all data were captured electronically and presented anonymously. Gatekeeper permission was obtained from the institution (IALCH) management to conduct the study.

## 3.5 Statistical analysis

Descriptive statistics were used to summarise the data. Percents and frequencies were used to summarise categorical variables. Patients were categorized into two groups: completed treatment (yes/no). Means (standard deviations) were used to summarize numeric data for pre and post time points, such as FVC, 6 minute walk, WCC and ESR and medians (IQR) for CRP. The rate of change was calculated as a rate : pe/post test results. A one sample test was used to test if the mean change rate for each group was equal to zero and a two-sample t test used to compare the mean change between the two groups. The change rate was then categorised into: worsened (<-10%) and improved/static >-10% and logistic regression used to compare the two groups. Odds ratios, 95% CI and p values are reported. Ordinal variables such as NYHA and HRCT scans were categorized into improved/static and progression and logistic regression used to compare treatment groups. Data was analysed using Stata V15.1.

# CHAPTER FOUR: RESULTS

All 62 subjects received CYC for the treatment of CTD-ILD. The treatment plan was to complete 18 doses of treatment over a nine month period. However, not all patients were able to complete all the cycles.

## 4.1 The prevalence of patients with CTD-ILD who were treated with CYC.

During the study period (2009-2018), 62 subjects met the inclusion criteria.

## 4.2 Demographics

The majority of these patients were female (88.7%; n=55). The predominant age group was between 40 and 59 years old. Most patients were Black Africans (50%; n=31) followed by Indians (43.5% ; n=27) and then Whites (6.5%; n=4). (Table 7,8,9). There were no patients from the Coloured racial group.

**Table 7: Age**

| | n | % |
|---|---|---|
| 20-39 | 8 | 12.9 |
| 40-59 | 40 | 64.5 |
| 60-69 | 14 | 22.6 |

**Table 8: Sex**

| | n | % |
|---|---|---|
| Male | 7 | 11.3 |
| Female | 55 | 88.7 |

**Table 9: Race**

| | n | % |
|---|---|---|
| Black | 31 | 50 |
| Indian | 27 | 43.5 |
| White | 4 | 6.5 |

## 4.3 Classification of connective tissue disease

The commonest connective tissue disease associated ILD was SSc-ILD (59.7%), followed by MCTD-ILD (12.9%), SLE-ILD (11.3%), UCTD-ILD (3,2%) and other connective tissue associated lung diseases. Eg. sine scleroderma, rheumatoid arthritis, sjogren's syndrome and idiopathic inflammatory myopathy (12.9%).

**Table 10: Type of CTD**

| Diagnosis | n | % |
|---|---|---|
| Systemic sclerosis | 37 | 59,7% |
| Mixed connective tissue disease | 8 | 12,9% |
| Systemic lupus erythematosus | 7 | 11,3% |
| Undifferentiated connective tissue disease | 2 | 3,2% |
| Other | 8 | 12,9% |
| **Total** | **62** | **100,0%** |

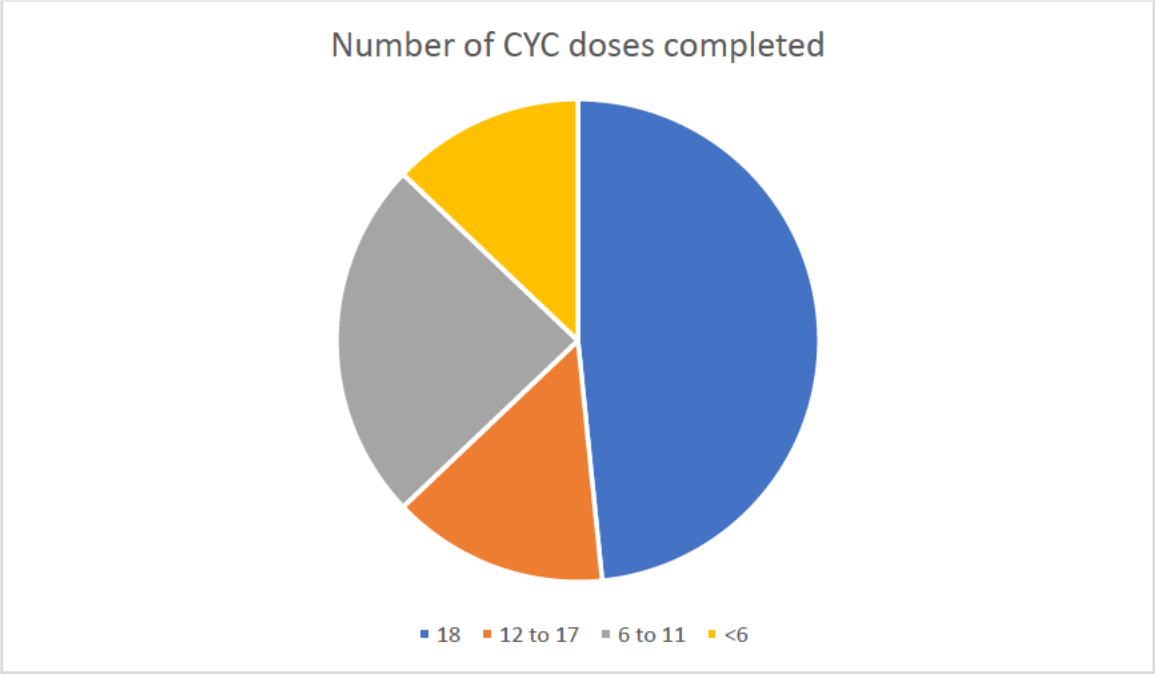
### 4.4 Number of CYC doses completed

The percentage of patients that completed 18 cycles of CYC treatment was 48,4% (n=30) with 12,9% (n=8) completing less than 6 doses.

**Table 11: Number of doses completed.**

| Number of cycles completed | n | % |
|---|---|---|
| 18 | 30 | 48,4% |
| 12-17 | 9 | 14,5% |
| 6-11 | 15 | 24,2% |
| < 6 | 8 | 12,9% |
| Total | 62 | 100,0% |

**Fig 9 : Number of CYC doses completed**



### 4.5 Presenting symptoms and functional status

#### *4.5.1 Presenting symptoms*

Symptoms were recorded at initial visit and post CYC treatment. The commonest presenting symptoms were cough and dyspnoea (41.9%;n=26)). Only 8 patients presented with cough only (12.9%) and 14 patients presented with dyspnoea only (22.6%). Eight patients did not have any respiratory symptoms (12.9%) and only one patient had a combination of cough, dyspnoea and chest pains on presentation. There was no symptom documentation for three patients. (Table 12).

**Table 12: Presenting symptoms**

| | **Pre Treatment** | | **Post Treatment** | |
|---|---|---|---|---|
| | N | % | n | % |
| Cough and dyspnoea | 26 | 41,9 | 11 | 17,7 |
| Dyspnoea | 14 | 22.6 | 29 | 46.8 |
| Cough | 8 | 12,9 | 8 | 12,9 |
| Cough, dyspnoea and chest pains | 1 | 1,6 | 0 | 0 |
| Chest pain | 1 | 1.6 | 2 | 3,2 |
| Other | 8 | 12.9 | 11 | 17.7 |
| Asymptomatic | 8 | 12,9 | 11 | 17,7 |
| Not documented | 3 | 4.8 | 0 | 0 |
| | | | | |
| Total | 62 | 100 | 62 | 100 |

#### *4.5.2 Functional status*

The New York Heart Association (NYHA) functional class was documented at presentation and post treatment. At presentation 1 patient (4.55%) was class 1 disabled, 27 patients were class II disabled (43.5%), 28 patients were class III disabled (45.2%) and 3 were class IV disabled (4.8%). Three patients were not documented (Table 13).

**Table 13: NYHA classification pre and post CYC treatment**

| | **PRE** | | **POST** | |
|---|---|---|---|---|
| **NYHA** | **n** | **%** | **n** | **%** |
| I | 1 | 1,6% | 5 | 8,1% |
| II | 27 | 43,5% | 34 | 54,8% |
| III | 28 | 45,2% | 6 | 9,7% |
| IV | 3 | 4,8% | 5 | 8,1% |
| Not documented | 3 | 4,8% | 12 | 19,4% |
| Total | 62 | 100,0% | 62 | 100,0% |

The NYHA outcome was analyzed post treatment. This excluded the 3 patients that had no pre and post documented. From the 25 subjects that completed treatment, 89,3% showed improved or static NYHA. Of the 18 that did not complete treatment, 85,7% showed an improvement or

static NHYA post treatment. Only 12.2% did not improve. The chances of improving are slightly better for patients completing treatment compared to those patients that did not complete treatment. This was not statistically significant. (95% CI; 0,3 ; 7,7 ;P=0.707) (Table 14).

**Table 14: NYHA outcome pre and post CYC treatment**

| | **NYHA change** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Improved/ static** | | **Worsened** | | **Total** | | | |
| | **pre >= post** | | **pre < post** | | | **Odds of improving** | | |
| | **(n = 43)** | | **(n =6)** | | **(n = 49)** | **p value** | **OR** | **95% CI** |
| **Completed treatment** | **n** | **%** | **n** | **%** | | | | |
| No | 18 | 85,7% | 3 | 14,3% | 21 | | ref | |
| Yes | 25 | 89,3% | 3 | 10,7% | 28 | 0,707 | 1,4 | 0,3 7,7 |
| Total | 43 | 87,8% | 6 | 12,2% | 49 | | | |

### 4.6 Pulmonary function tests

Forced vital capacity (FVC) and six minute walk test (6MWT) were recorded pre and post CYC treatment. The majority of patients had a restrictive pattern. Diffusion test results were not documented in most patients and therefore they were excluded from the statistical analysis.

*FVC*

The FVC values were collated for each subject and analyzed pre CYC treatment and post CYC treatment. The forced vital capacity values were recorded in litres. (*l*) (Table 15).

**Table 15: FVC range**

| | **PRE** | | **POST** | |
|---|---|---|---|---|
| ***l*** | **N** | **%** | **n** | **%** |
| >2 | 9 | 15% | 8 | 13% |
| 1-2 | 30 | 48% | 32 | 52% |
| <1 | 17 | 27% | 11 | 18% |
| not documented | 6 | 10% | 11 | 18% |
| Total | 62 | 100% | 62 | 100% |

The average FVC for all patients irrespective of those that had a pre and post had a mean FVC of 1.40 (SD 0.62) pre-treatment and 1.54 (SD 0.73) post treatment.

A total number of 49 subjects had both the pre-treatment FVC and post treatment FVC documented and the mean was calculated. The mean FVC was 1,43 l pre-treatment (SD0.56)

and 1,50 *l* post treatment (SD 0,66). Of these 49 subjects the mean change in FVC was 0.07 (SD 0.50). The p-value was 0.33 and was not statistically significant.

We analyzed the FVC percentage change for those that completed treatment and those that did not complete treatment (Table 16). This excluded the 21 subjects who had missing values. A change of 10% in the FVC was used as a reference to determine if static, reduced or increased. A total of 71.4% of subjects showed improvement or had static FVC and 28,6% had shown progression of disease. The FVC change rate demonstrated a wide CI and a statistically insignificant P value (p value 0.9). There was no difference in outcome between those that completed 18 cycles CYC treatment and those that did not complete CYC treatment. There was no statistical significant difference.

**Table 16: FVC percentage change**

| | **Improved/ Static** | | **Worsened** | | **Total** | **P valu e** | **OR** | **95 % CI** | |
|---|---|---|---|---|---|---|---|---|---|
| | **pre <= post** | | **pre > post** | | | | | | |
| | **(n = 35)** | | **(n=14)** | | **(n = 49)** | | | | |
| **Completed treatment** | **n** | **%** | **n** | **%** | | | | | |
| No | 15 | 71,4% | 6 | 28,6% | 21 | | ref | | |
| Yes | 20 | 71,4% | 8 | 28,6% | 28 | 0,9 | 1,0 | 0,3 | 3, 5 |
| Total | 35 | 71,4% | 14 | 28,6% | 49 | | | | |

*4.6.2 Six Minute Walk Test (6MWT)*

Thirty-two patients had their 6MWT recorded at baseline. The test was not performed in the other 30 patients due to technical issues or due to functional disability. The mean 6MWT distance was 311.88m (SD128.83) pre-treatment and 350.64m (SD131.70) post. Sixteen subjects had both the pre and post-test 6MWT documented. The mean change was 34.69 with a SD of 111.94 and P value of 0.23.

For those subjects that completed treatment, 72,7% were static or showed improvement and 27,3% had a decline in their 6MWT. The values were *0 % and 20 % respectively in the group that did not complete treatment. The OR was 0,7 with CI (0,1-8,6). P value 0.7 (Table 17)

There was no difference in outcome between those subjects that completed treatment and those that did not complete treatment.

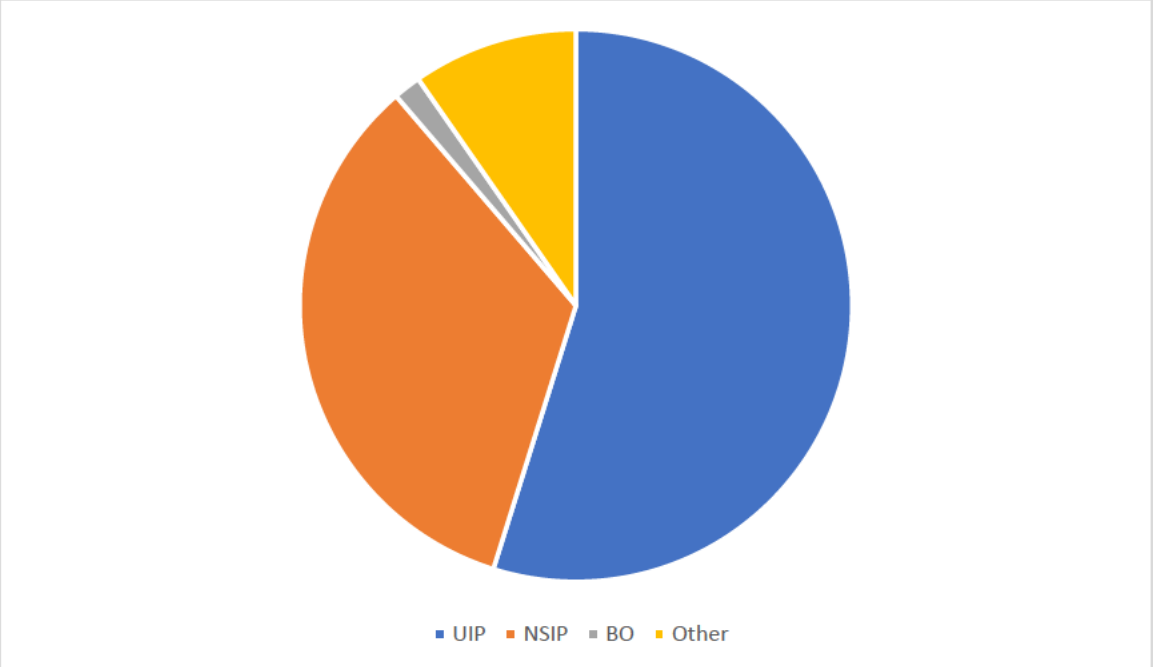
**Table 17: 6MWT change rate**

| Completed treatment | Improved/static pre <= post (n = 35) | | Worsened pre > post (n=14) | | Total (n = 49) | p value | Odds of improving OR | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | 0,8 | 0,7 | 0,1 – 8.6 |
| No | 4 | 80,0% | 1 | 20,0% | 5 | | | |
| Yes | 8 | 72,7% | 3 | 27,3% | 11 | | | |
| Total | 12 | 75,0% | 4 | 25,0% | 16 | | | |

### 4.7 High resolution computed tomography scan (HRCT Scan)

HRCT scan analysis demonstrated the following specific patterns of ILD: the majority had UIP pattern (55%; n=34) followed by NSIP pattern (34%; n=21), bronchiolitis obliterans (2%; n=1) and other patterns (10%; n=6) (Figure 10).

**Figure 10: Specific patterns of CTD associated ILD**




For those subjects that completed treatment (n=30), the majority showed an improved or static HRCT scan post treatment (83,33%) and only 13,33% showed radiological progression of disease. 3,33% were lost to follow up and there were no deaths.

In the cohort that did not complete treatment, 56,3% demonstrated a static or improved HRCT scan. Three patients demised prior to completion of treatment.

The P value was 0.9 and the OR was 1.0; hence, there was no statistically significant difference (Table 18).

**Table 18: HRCT scan outcome post treatment (including all subjects n=62)**

| | **Completed treatment** | | | | | |
|---|---|---|---|---|---|---|
| | **Yes** | | **No** | | **Total** | |
| | **(n = 30)** | | **(n = 32)** | | **(n = 62)** | |
| HRCT post CYC | **n** | **%** | **n** | **%** | n | % |
| Improved/static | 25 | 83,33 | 18 | 56,3 | 43 | 69,4 |
| Progression | 4 | 13,33 | 3 | 9,4 | 7 | 11,3 |
| No follow up | 1 | 3,33 | 8 | 25,0 | 9 | 14,5 |
| Demised | 0 | 0,0 | 3 | 9,4 | 3 | 4,8 |
| Total | 30 | 100 | 32 | 100 | 62 | 100,0 |

The data for 50 patients was analyzed. This excluded the 9 patients that were not followed up and the 3 that demised. For those that completed treatment 86,2% demonstrated improvement or had a static HRCT scan post treatment. A total of 13,8% of this group had progressive lung disease. There was minimal change for the group that did not complete treatment. In this group 85,7% showed improvement or static disease and 14,3% showed progressive disease. P value 0,9; OR 1,0; 9%%CI 0,2-5,2 (Table 19). The chances of HRCT scan improving or remaining static were same whether the patient completed treatment or not.

**Table 19: HRCT scan post treatment (excluding those that did not have both a pre and post scan n=50)**

| | **Improvement/ Static** | | **Progression** | | **total** | | Odds of improving | | |
|---|---|---|---|---|---|---|---|---|---|
| | **(n = 43)** | | **(n =7)** | | **(n=50)** | **p value** | **OR** | **95% CI** | |
| **Completed treatment** | **n** | **%** | **n** | **%** | | | | | |
| No | 18 | 85,7% | 3 | 14,3% | 21 | | ref | | |
| Yes | 25 | 86,2% | 4 | 13,8% | 29 | 0,9 | 1,0 | 0,2 | 5,2 |

### 4.8 Side effects during treatment

Almost two thirds of patients on treatment did not exhibit any significant side effects. 8% developed an infection, 4.84% had chest pains during infusion of the drug which resolved after the infusion was completed, 4,84% had a combination of infection with pruritis, 3.2% developed generalised pruritis, 1.61% had a cough only and 1.61% had nausea and vomiting

during administration of treatment (Table 20). In general, the patients tolerated the side effects well. Symptomatic treatment sufficed.

**Table 20: Side effects during CYC treatment**

| | n | % |
|---|---|---|
| Nausea/Vomiting | 1 | 1,61 |
| Chest pains | 2 | 4,84 |
| Infection | 5 | 8,06 |
| Headache/Pruritis | 2 | 3,23 |
| Generalised Pruritis | 2 | 3,23 |
| Infection/Pruritis | 3 | 4,84 |
| Other | 5 | 8,06 |
| No side effects | 40 | 64,52 |
| Cough | 1 | 1,61 |
| Total | 62 | 100 |

## 4.9 Inflammatory markers

WCC, CRP and ESR were recorded pre-treatment and post treatment.

### *4.9.1 White Cell Count (WCC)*

60 patients had a documented WCC prior to treatment and 57 patients had a documented WCC post treatment. Prior to treatment 91,7% had a normal WCC and 8.3% had an elevated WCC. We used a reference range of <15 (normal) and > 15 (elevated).

Of the 57 patients that had both a pre and post treatment WCC, 54.39% had a decline of 10% in their WCC, 28.07% remained static and 17.54% had increased their WCC.

We analysed the WCC change for those patients that had a documentation for both pre and post treatment (n=57). The mean WCC pre-treatment was 9,4 (SD 3,65) and post treatment was 7,93 (SD 3,54). The mean change between the two values was -0,14(SD 0,25;p value 0,001). This was statistically insignificant.

### *4.9.2 C-reactive Protein (CRP)*

61 patients had a documented CRP prior to treatment (IQR 5-25) and 55 patients had a documented CRP post treatment (IQR6-29). Since CRP is not normally distributed we used the Median. The median CRP for the pre-treatment group was 13 and 11 for the post treatment group. The mean for the pre-treatment group was 22,95(SD 33,06) and 23,24 (SD 30,10) for the post treatment group.

49 patients had both a pre and post test result documented. The median change in CRP was -0,05 with a P value of 0,65. (n=49) which was not statistically significant.

50.8%(n=31) had a normal CRP prior to treatment and 49.2% (n=30) had an elevated CRP prior to treatment.56.4% (n=31) had a normal CRP post treatment and 43.6% (n=24) had an elevated CRP post treatment.

CRP had no significance in this cohort.

### *4.9.3 Erythrocyte Sedimentation Rate (ESR)*

58 patients had a documented ESR prior to treatment and 50 patients had a documented ESR post treatment. We used a reference of <15 (normal) and > 15 (elevated). 46,81% (n=22) showed a pre-treatment ESR that was lower than the post treatment, 12,77% remained unchanged and 40,43% showed a higher than the post treatment.

The ESR change was documented for both pre and post in 47 subjects. The mean pre-treatment was 40,94 (SD 32) and 36,70 (SD 25,72) post treatment. The Mean change was -4,23 (SD 21,1) with a P value of 0,18. The ESR changes were statistically insignificant.

### *4.10 Steroids*

All 62 patients were on oral corticosteroids during treatment with CYC (Prednisone 5mg to 15mg daily). No patients required higher doses of steroids during treatment.

### *4.11 Complications of ILD*

72.6 % of patients had PHT with cor-pulmonale on echocardiography. 27,4% had other co-morbidities unrelated to ILD.

### *4.11 Outcome*

The administration of CYC treatment to patients with CTD-ILD had a trend towards benefit but it did not reach statistical significance. 59.7% (n=37) of patients demonstrated no progression of disease, 17.7% (n=11) showed progression of disease, 6.5% (n=4) demised and 16.1% (n=10) were lost to follow up.

**Results summary:**

Sixty-two patients were seen in the Pulmonology department at IALCH as either an inpatient, outpatient or both during the period January 2009 to December 2018. The majority of these patients were female of black origin and aged between 40 to 59 years. Most of the patients in this study had systemic sclerosis associated interstitial lung disease. This accounted for 58,1% of these patients. A total of 48,4% of patients completed the full 18 cycles of CYC treatment and 51,6% did not complete treatment. The most common HRCT scan pattern of disease was UIP, which accounted for 55% of all ILD in this group.

We analysed the results according to those that completed nine months of treatment (18 cycles) and those that did not complete nine months of treatment and compared this to published studies from other regions of the world. According to the data analysis, there was a trend towards clinical benefit for those that were treated with cyclophosphamide based on NYHA and HRCT scan findings. However, there was no statistical significance for those that completed 18 months verses those that did not complete treatment. 89,3% of patients that completed treatment and 85,7% of patients that did not complete treatment had an improvement in dyspnoea class by the end of treatment.

In summary, the local effects of CYC treatment for the management of ILD showed a trend towards clinical benefit irrespective of the duration of treatment but no statistical significance.

# CHAPTER FIVE: SYNTHESIS / DISCUSSION

## 5.1 Discussion

Systemic Sclerosis has the highest mortality of all the connective tissue diseases. It accounted for 59,7% (n=37) of patients in this study of 62 patients, followed by MCTD (12,9%;n=8) and SLE (11,3%;n=7). Although the pathophysiology of SSc has been studied over the last 238 years, the morbidity and mortality of this disease has not changed. Treatment options remain limited. [8]

There is still no definitive treatment for CTD-ILD despite multiple trials. However, cyclophosphamide is the generally accepted treatment of choice for patients with progressive or severe CTD-ILD. This was borne out of Scleroderma-ILD studies.[34]

CYC and mycophenolate mofetil (MMF) are the two drugs that have been well studied. The two are currently used as first line treatment based on limited data. According to the latest international trends, the use of corticosteroids remains of doubtful benefit and monotherapy or chronic use is not advocated. [34]

The majority of these patients were female (88,7%) which is in keeping with most international studies and within the 40-59 year old age group. In this study, we found that 50% of patients were of African black origin and 43,5% were of ethnic Indian origin and only 6,5% were whites. The population demographics of South Africa, being a multi-racial society, encompasses more than 80% black Africans, 8,4% whites, 8,8% coloureds and only 2,5% Indians. There is a disproportionately large group of Asian Indians in this study. This may be due to referral bias, or genetic factors that may play a role in connective tissue diseases or that KZN has a higher concentration of Indians. The 5-year survival rate was 95%. According to international data the 5 year survival is between 82-90% and 10 year survival 29-69%.[56]

To our knowledge, this is the first study that has focused on the prevalence and local effects of administering 18 cycles of CYC treatment over a period of 9 months for the management of CTD-ILD in KZN, South Africa. Ashmore did a similar study in 2017. This study was conducted on patients with systemic sclerosis only, at a tertiary institution in Gauteng. These patients had ILD.

The demographics in that region correlated with ours in KZN as the majority of patients were female of black ethnicity with a mean age of 44 years. [57] Our study included patients with other connective tissue diseases that were treated with CYC. Ghammo et al did a local KwaZulu Natal study in 2020 in patients with RA-ILD. However, there was no comment on CYC treatment and other CTD's. [58]

Previous studies have highlighted the treatment period over 6 months and 12 months. None of these studies showed significant impact on disease outcome. An example of a one year study was the first scleroderma lung study (SLS 1) which showed clinical improvement. The patients in this study were followed up for one year after discontinuing treatment. Disappointingly, symptoms recurred after one year. Further studies are therefore required. [41]

A total of 48,4% patients completed treatment and 12,9% had less than 6 doses. The observation that more than half the patients did not have the full 18 cycles as planned reduces the power of our study significantly. It becomes difficulty to make firm conclusions. Further research is required to determine the causes for the noncompletion of the 18 cycles as per our local protocol. Studies on reasons for noncompletion of treatment are needed for firm conclusions to be made. Possible explanations include socio-economic challenges, lack of transport, poor understanding of the connective tissue diseases as a group, lack of patient education programs and side effects of treatment.

We evaluated the presenting symptoms and patients with a combination of cough and dyspnoea accounted for the majority of the cases (41,9%) and only 12,9% were asymptomatic. There was an 89,3% static or improved rate in those that completed treatment and a 85,7% static or improved rate in those that did not complete treatment. There was clinical significance but not statistically significant improvement (P value 0,707: CI 0,3-7,7; OR 1,4). This suggests a "protective effect" of treatment, but the confidence intervals on estimated rates for this group was too wide to exclude the possibility of no treatment effect.

For those patients that had both pre and post FVC's documented (n=49) the mean FVC pre-treatment was 1,43*l* (SD 0,56) and 1,50*l* post treatment (SD 0,66). The Mean change was 0,07*l* (SD 0,50;p value 0,33). There was no statistically significant change in the FVC on this subject group. Absolute FVC values (in litres) were used instead of percentage predicted. This is particularly of significance as most patients were black African and female.

It may be that CYC treatment in CTD-ILD can prevent disease progression, improve quality of life and reduce relentless progression to death. These clinical benefits may possibly be seen in those patients who have had as few as six cycles.

32 patients had a documented 6MWT. The missing data was due to a number of factors. These included poor clinical condition at the time the 6MWT had been scheduled, failure to capture electronic data and failure to order the test. In healthy subjects, the 6MWT distance ranges from 400m to 700m taking into account the main predictor variables being gender, age and height. Our patients had a mean of 311,88m pre-treatment and 350,64m post treatment. However, not all subjects had both a pre and post treatment 6MWT documented. Only 16 patients were in this group. The mean 6MWT distance was 320m (n=16) pre-treatment and 354,69 (n=16) post treatment. No firm conclusions can be drawn from the 6MWTin this study.

The minimal important difference (MID) in 6MWT is generally accepted to be 30m for adult patients with chronic respiratory disease. There is some variability across studies and methods to determine the MID; however, based on the large evidence base now available, we can be confident that the MID lies between 25 and 33 m.[59] The mean change in this study was 34,69 m (SD 111,94;p value 0,23).This demonstrated an improvement of 34,69m.

The gold standard for diagnosing CTD-ILD is by HRCT chest. [55] According to a recent study in 2020 by Gao and Moua, NSIP is the predominant pattern. NSIP is present in more than half of all patients with SSc-ILD, followed by UIP.[36] Another study done by Corte et al had 101 patients who had a lung biopsy. 21% in this study had a confirmed connective tissue disease. 2/3 of these patients had NSIP and 1/3 had UIP [60]. In our study, the majority of patients had a UIP pattern (55%), followed by NSIP (34%). A local study of Rheumatoid arthritis associated ILD by Ghammo *et al* demonstrated a predominant UIP pattern on HRCT scan [58]. The HRCT patterns in our local population seem to be different to those reported elsewhere. The UIP pattern on HRCT may be more predominant in South Africa. The UIP pattern is generally associated with poorer prognosis. [61] Further research is required looking at long-term prognosis in our patients.

Fifty-three patients had both a baseline scan and a post treatment scan. 9 were lost to follow up (3 patients demised and 6 patients did not come back). For those patients that were followed up and completed treatment there was a static or improved HRCT scan in 86,2%. For those that did not complete treatment there was a static or improved HRCT scan in 75%. (P value 0,3; OR 2,1; 95% CI : 0,5-8,5). The chances of improving are twice as great if treatment is completed but this did not reach statistical significance.

Most patients did not exhibit any significant side effects during treatment (64,52% of the group). A small number suffered from infection and pruritis. 4,84% of patients developed chest pains during the CYC infusion but resolved once treatment was completed. From our reading, this appears not to have been documented in the literature before. Further research is required to

determine the pathophysiology of the chest pain during CYC infusion. Particularly interesting would be studies looking at the coronary and pulmonary circulations.

Inflammatory markers and WCC remained relatively normal in this cohort. This attests to the safety and tolerability of IV cyclophosphamide used in this treatment protocol.

A large proportion of patients in this study had pulmonary hypertension (72,6%). This finding is in line with reports from other studies. [51] . 4,8% demised during treatment. The cause of death was advanced lung disease. Aggressive immunosuppressive agents, such as rituximab, are reserved for patients with refractory, severe, or rapidly progressive disease. None of our patients received rituximab. Possible explanations include non-availability, access issues or no indication. Regrettably, randomized controlled trials remain lacking for most CTD-ILD studies and the current treatment options are from observational studies and case series. Biological agents, antifibrotic drugs and stem cell transplants are considered treatment options in CTD-ILD. Further research is required in order to make firm conclusions on their usefulness.[36]

### 5.2 Conclusions

The treatment of connective tissue associated interstitial lung disease remains challenging with limited options. This retrospective study analysed a group of 62 patients that were treated with CYC. This is the first study to our knowledge, in South Africa, to determine the demographics and treatment outcomes for patients who were treated with CYC 2 weekly for 9 months (18 doses).

The overall conclusion is that despite clinical improvement, the use of 18 doses of CYC, every 2 weeks, did not result in significant disease regression. However, CYC seems to halt disease progression. Patients tolerated the treatment well.

## 5.3 Limitations of study

There are a number of limitations in this study. Firstly, the study is retrospective. Referral bias is inevitable. Missing or incomplete data was a major challenge. There may be inconsistencies in capturing of clinical, laboratory and radiological data. The presenting symptoms, NYHA classification and side effects during treatment may not have been recorded accurately as the clinical notes were based on various doctor's opinions. The clinical assessments were not standardised. There are inherent weaknesses in retrospective clinical studies where symptoms and physical signs are important parameters.

The lack of a control group in this study is acknowledged. However, it would be very difficult, ethically, to justify having a control group; that is to say a cohort of patients with ILD who are not given CYC. This is because overtime these patients do very badly without some form of definitive intervention. There is progressive loss of lung function and worsening of symptoms. Methodologically this is probably the best way to conduct this form of study.

There is very little published data in South Africa and world-wide to compare. This would have made the discussion more interesting and robust.

The connective tissue diseases were lumped together because the number of patients is very small. These diseases are not common. If we sub analyse according to each CTD the numbers will be too small to make statistical sense. If there were hundreds of patients with connective tissue disease locally, or a multinational international study, then sub-group analysis would be possible.

Lastly, this study is limited to one institution. Inkosi Albert Luthuli Central Hospital is the referral for all hospitals in the public sector in KwaZulu Natal. It provided quaternary level care for an estimated population of 11,384,700 in 2018. This may not truly represent the greater population of South Africa. However, the study contributes to our knowledge of CTD-ILD.

### 5.4 Recommendations

Further prospective multicentre randomized trials are required to determine the optimal drug treatment to manage patients with CTD-ILD in South Africa.[36] There is a clear need to scale up research in the field of pathogenesis of CTD ILD. The knowledge is crucial in designing new treatment options. This will assist physicians to administer tailored treatment.

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