A COMPREHENSIVE EXPLORATION OF MANAGING UNCLASSIFIABLE INTERSTITIAL RESPIRATORY DISORDER

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Abstract:
The purpose of the current research was to review the available medical literature to evaluate various therapy options for unidentified interstitial lung disorders. Between 2010 and 2020, the literature was checked out using the Embase, PubMed, Medline, PubMed, and Ovid databases. 15% of individuals with interstitial reparatory disorder diagnosis had unclassifiable interstitial lung illnesses. As a result, it comprises a significant fraction of patients who need to be treated by a specialist team. Due to the variety of patients, unclassified interstitial lung illnesses are more challenging to confirm the diagnosis of than other forms of interstitial lung diseases. A combination of "management" or "treatment" and "unclassified interstitial lung disorders" or "UILD" and "outcome" was included in the search phrases. After this, findings were further narrowed to only include recent original research articles on the management of unclassified interstitial lung disorders. Selected studies included information on the medication's nature and treatment results. 589 studies in all were located. 27 publications were discovered after animal-related studies were excluded and only human trials were included. With a total of 1053 individuals with unexplained interstitial lung diseases, seven articles were determined to be qualified. Four studies—three of which were multi-center—were double-blind, randomized controlled trials. Two studies were case reports, while one research was retrospective. According to the study, nintedanib and pirfenidone (as monotherapy or in combination) are the two most effective treatments for unidentified interstitial lung disorders. It is necessary to conduct more trials with a sound design to investigate prospective intravenous cyclophosphamide and immunotherapy treatments.

Keywords: respiratory, lung, unclassified

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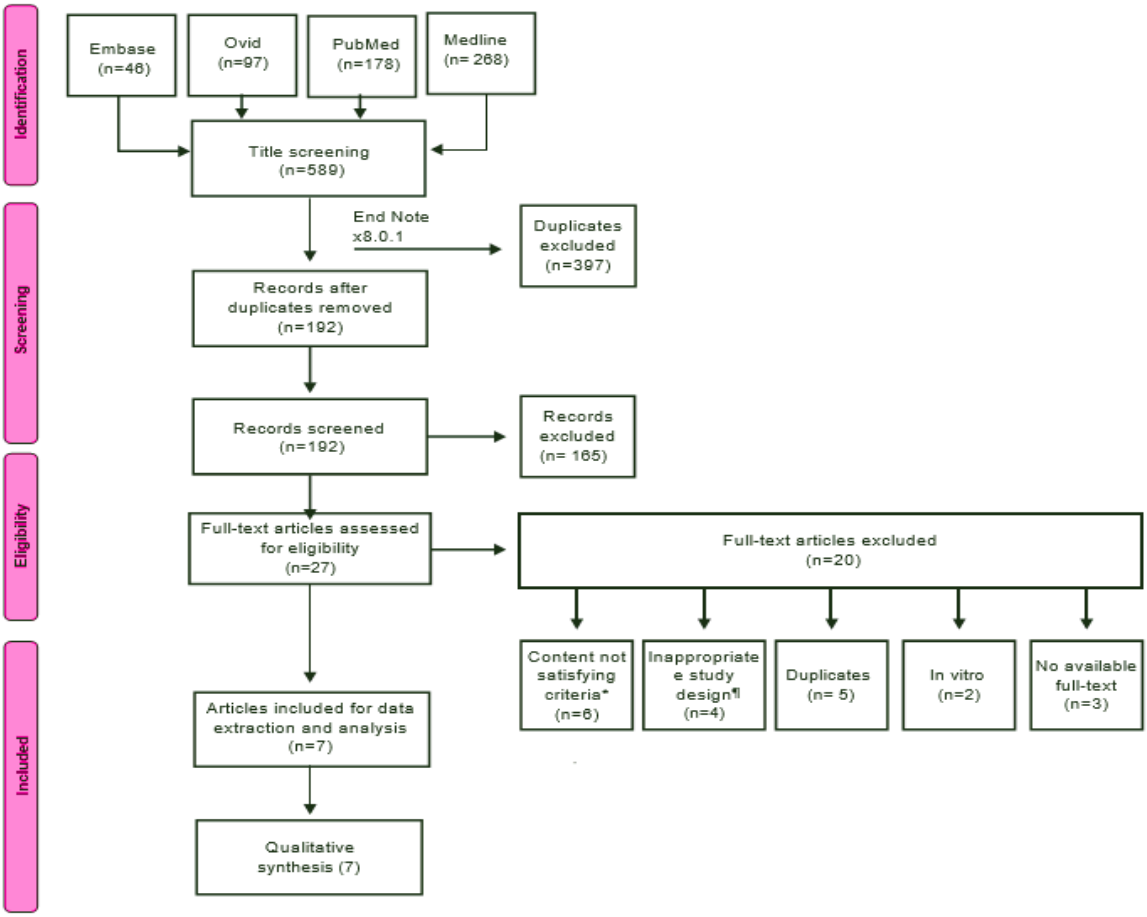
Introduction:

Many disorders that result in fibrosis or inflammation of the pulmonary parenchyma make up interstitial lung disease (ILD), which is divided into several subtypes. [1] ILD may have several different causes, however, some instances are idiopathic. [2] Idiopathic ILD is a challenge to doctors since it is difficult to diagnose and treat. [3] Because of the clinical manifestations that may accompany ILD's respiratory symptoms, a multidisciplinary team is needed to diagnose and characterize ILD. [4] Nonetheless, a lot of individuals have difficult diagnoses and are given an unclassified ILD diagnosis. [5] This instance is common, particularly for certain ailments like chronic hypertensive pneumonitis, fibrosis, ILD, and connective tissue disease-associated-ILD (CTD-ILD). [6] Patients with unidentified interstitial lung disease will exhibit both the clinical signs of interstitial pulmonary fibrosis and non-fibrotic ILD since it is a heterogeneous illness made up of undiscovered fibrotic ILDs. [7,8] Among these frequent clinical symptoms include autoimmune illness, dyspnea, and dry cough. Pharmacological and non-pharmacological therapies are used to treat unclassifiable ILD. [9,10] The non-pharmacological therapies consisted of vaccinations, extra oxygen, smoking cessation, vaccinations, extra oxygen, and pulmonary rehabilitation. [11] Unclassified interstitial lung disease may also be treated with medicines. Lung transplantation should only be used as a final option in situations of resistance. [12] The drugs used to treat this difficult form of ILD, however, have been the subject of discussion in recent years. [13,14]This systematic review's objective is to examine the literature over the last ten years for management outcomes of unclassified interstitial lung disease.

Methodology:

This literature review was conducted using the PRISMA checklist by its guidelines for meta-analysis and systematic reviews. To find suitable studies from 2010 to 2020, this systematic review searched 4 databases, including Ovid, Pubmed, Embase, and Medline.



Search Technique: "Unclassified Interstitial Lung Diseases" or "UILD", "Treatment", "Management" and "outcome" were among the search phrases used. We carefully assessed each of the abstracts and titles that emerged as a consequence of the main search to verify that no appropriate publications were overlooked. Next, only recent

original research papers that examined treatment plans for unclassified interstitial lung illnesses were included in the findings. Also, the chosen studies included information on the kind of drug used and how effectively it worked to treat patients. All research methodologies from different nations were also included. Only papers that were written in English were identified as relevant studies, and they may now be examined in more detail in the next stage.

Inclusion Criteria: At this step, the inclusion criteria for choosing the papers to be reviewed in the systematic review were established. To choose which abstracts to take into account, each one was personally evaluated. The inclusion criteria required that there be sufficient details on the kind of medicine used and the result of the therapy. Moreover, studies with individuals who were adults exclusively were considered. Also, the references of chosen trials were looked through to determine if any papers were comparable. Ultimately, the final list of qualified publications was used to gather and summarize the necessary data sets. Studies were eliminated for a variety of reasons, including in vitro or animal participation, duplicate or incomplete information, a dearth of full-text journals, or a bad research design. The full search procedure is shown in detail in Figure 1.

Researcher	Reference no	Year	Treatment Type	Aim	Results
Yokohoriet al.	[15]	2017	Combination of erythromycin and pirfenidone	To evaluate the effectiveness of pirfenidone combination treatment at 1,200 mg/day Moreover, erythromycin 400 mg/day in unclassifiable interstitial pneumonia linked with bronchioloalveolar disease (HABA).	The treatment of interstitial pneumonia caused by HABA improved with erythromycin. While the pulmonary functions, oxygen saturation, and exertional dyspnea did not worsen, the CT findings of GGO and Broncho vascular bundle-dominant reticular shadows did six months following the beginning of the pirfenidone medication. For over 2 years, this combination treatment has been used, and chest CT scans and dyspnea with exercise have not changed or shown any abnormalities.
Koga etal.	[16]	2018	Intense immunotherapy	To explain how an anti-MDA-5 antibody was administered to a unclassified interstitial pneumonia patient.	Treatment with tacrolimus and intravenous cyclophosphamide (IVCY; 840 mg (500 mg/mm2)) was repeated every two weeks with an increase in IVCY dose to 900 mg. Also administered was high-dose intravenous immunoglobulin. The hypoxia started to get better after the fourth cycle of intravenous cyclophosphamide (IVCY) treatment (each cycle every two weeks), and after two months in the hospital, the blood ferritin levels dropped to 767 ng/mL. The effects of high-dose steroid treatment were ineffective.
Wiertz etal.	[17]	2018	pulse treatment with intravenous cyclophosphamide	To investigate the results of a 6-month ICPT in individuals with corticosteroid-resistant uILP	When ICPT began, all patients were resistant to corticosteroids. The impact of therapy was less obvious and showed a decline in the illness rate in IIP patients who could not be classified. An unremarkable decrease in FVC was seen. Six months after the start of ICPT, the FVC decreased from 18.2% to 5.9% (p=0.241). After 12 months, all 13 unclassifiable IIP patients who underwent ICPT showed a persistent improvement in FVC. Consolidation treatment, however, included a variety of drugs, including corticosteroids, MMF, azathioprine, and rituximab. Patients with unclassifiable IIP who were steroid-refractory showed a substantial improvement in FVC after receiving ICPT.
Maher etal	[18]	2019	Pirfenidone	To investigate the effectiveness and safety of pirfenidone (2403 g/day) in treating progressive fibrotic unclassified ILD over a six-month period in comparison to placebo.	With adequate safety and tolerability, pirfenidone is beneficial in individuals with progressive fibrotic unclassified ILD during a six-month period. Pirfenidone has to be studied further clinically in individuals with fibrosing unclassified ILD, nevertheless. Daily home spirometry can't be employed as the main outcome metric until further research is done. Individualized therapy is necessary for unclassified ILD patients since they are regarded as a diverse patient group.
Kreuter etal.	[19]	2020	Pirfenidone	To talk about a subgroup evaluation for individuals with ILD that isn't characterized and who are also on mycophenolate mofetil	Notwithstanding the trial's general conclusion that pirfenidone is helpful in treating patients with progressive fibrosing unclassified ILD, this combination with MMF seems to suggest that pirfenidone has a different impact on FVC alteration (assessed through spirometry). Irrespective of the MMF control treatment, pirfenidone's safety profile remained consistent. These results need to be investigated in a wider patient population via more research.
Martinezet al.	[20]	2020	Nintedanib	To evaluate nintedanib's long-term safety in patients with ILD that is not yet categorized.	19.6% of patients receiving nintedanib had adverse events that resulted in treatment cessation, compared to 10.3% of patients receiving a placebo (p-value = 0.024). The most prevalent adverse event and reason for therapy cessation was diarrhea.
Wells etal.	[21]	2020	Nintedanib	To investigate nintedanib's safety and effectiveness in	When chronic fibrosis and FVC are improved, nintedanib may slow the pace at which unclassified ILD progresses (p value 0.001).

				treating individuals with unclassified ILD.	

Results:

In this research, we looked at 35 individuals who had had severe or penetrating trauma and developed traumatic diaphragmatic hernias. Congenital diaphragmatic hernia patients were not included in the research. Among the 35 patients, 24 showed up in the emergency room, while 7 showed up in our outpatient department after the initial trauma had already occurred and 4 were moved to our ward after being hospitalized in other units. Our patients ranged in age from 7 to 62 years old, although the majority were between the ages of 18 and 48, making up 68.9% of the sample.

The study's gender ratio was 2.2:1, with 24 men (68.57%) and 11 women (31.41%) participating. Just 4 patients (11.42%) had traumatic right-sided diaphragmatic hernias, making left-sided hernias the most common diagnosis (88.57%). Shortness of breath, nausea, and chest and abdominal discomfort were the most typical presenting symptoms. Physical examination revealed reduced air entry in 28 (80%) of the patients, and in 13 (37%) of the patients, bowel noises were audible in the chest.

The patients in our research suffered injuries in a variety of ways, with the majority (60%) being engaged in auto accidents. Additional reasons included falls, the collapse of a big item or a roof, and crush injuries. All patients had chest x-rays taken, and 27 (77%) of those instances resulted in a diagnosis. All patients underwent ultrasonography, with 30 (85.72%) of them showing positive findings at the time of presentation. In more complex situations, CT scans and fluoroscopy were performed and had a 100% accuracy rate for diagnosis.

Rib fractures were the most prevalent injury in traumatic diaphragmatic hernia, occurring in 12 (34.2%) of the patients, when we additionally examined the related injuries. Injuries to the limbs were discovered in 9 (25.71%) individuals, whereas splenic and liver injuries were discovered in 6 (17%) and 4 (11.4%) patients, respectively. 5 (14%) individuals had head injuries, compared to only 1 (2.85) patient who had pelvic fractures.

Discussions:

Unclassified interstitial lung disorders are a diverse set of illnesses that make diagnosis and therapy difficult. There is not enough information on the treatment results of people with UILD and the drugs used to treat UILD since it may be challenging to identify individuals with UILD.19 Patients with UILD often have various symptoms, including respiratory problems, which necessitates the cooperation of a multidisciplinary team. Using an analysis of the medical literature published in the previous ten years, the current study looked at the effectiveness and safety of the drugs used to treat UILD.

In this review, many drugs have been considered. In two trials, the use of nintedanib to treat UILD was investigated. In patients with UILD, Wells et al. [21] looked at the effectiveness and safety of nintedanib. Nintedanib effectively slowed the evolution of UILD, as shown by Wells et al. [21], by improving FVC and chronic fibrosis (p-value less than 0.001).

Martinez et al. [20] conducted a study to investigate the effectiveness of nintedanib over the long term. Martinez et al. [20] showed that the nintedanib discontinuation rate was considerably greater in the nintedanib group than that of the control group, with diarrhea being the most common reason for medication discontinuation.

Three studies also looked at pirfenidone as a single therapy or part of a combination therapy. Maher et al.' ‘s18 investigation of the six-month safety and effectiveness of pirfenidone monotherapy. Pirfenidone medication was shown by Maher et al.18 to have good effectiveness over six months in individuals with progressive fibrotic UILD and adequate safety and tolerability.

Kreuter et al. [19] investigated the effects of pirfenidone on individuals using Mycophenolate mofetil as a combination medication (MMF). According to Kreuter et al. [19], the combination did not substantially vary from monotherapy in regards to safety, but the effectiveness result was debatable.

A patient with a bronchioloalveolar disease (HABA)-associated UILD was the subject of a case study by Yokohori et al. [15] that detailed the effectiveness of the drug combination of pirfenidone and erythromycin. According to Yokohori et al. [15], even after two years, the combination continued to alleviate the patient's symptoms, including dyspnea with exercise and pulmonary functions.

Intravenous cyclophosphamide pulse therapy (ICPT) was a different therapeutic approach that Wiertz et al. [17] explored on patients with unclassifiable interstitial lung pneumonia who had failed to respond to corticosteroid therapy (UILP). According to Wiertz et al. [17], ICPT medication slowed the course of the illness and resulted in long-lasting improvement.

A patient with unclassifiable interstitial lung pneumonia was treated with intense immunotherapy in one case report by Koga et al. [16] utilizing anti-MDA-5 antibody together with

intravenous cyclophosphamide, an oral calcineurin inhibitor, and corticosteroids. In patients with UILP, Koga et al. [16] showed that early treatment of the suggested combination, before irreparable lung injury, may improve prognosis.

Despite the dearth of information on the treatment of uILD in the medical literature, the current systematic review included studies with strong study designs (four of which were double-blind, randomized controlled studies), which strengthens the review's conclusions and encourages additional research on the condition.

It should be emphasized that over the last three years, the management of UILD has received a great deal of attention, with an increase in newly published well-designed articles on the condition and a desire within the medical community to fill in the gaps in the UILD literature. This is regarded as the first systematic evaluation to assess the effectiveness of UILD therapy.

Conclusions:

The effectiveness of many drugs in treating UILD has been studied in recent years. Pirfenidone and nintedanib are the two drugs with the best prospects. Nevertheless, immunological therapy as well as intravenous cyclophosphamide pulse therapy are promising treatments that need to be further investigated using more reliable research designs. Except for an elevated rate of treatment discontinuation brought on by the occurrence of diarrhea with nintedanib, the safety of UILD medications is typically satisfactory.

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