Management of unclassifiable Interstitial Lung Diseases; A systematic review

Abdullah Rashed Alharbi

King Saud University, Kingdom of Saudi Arabia

Address for correspondence
Abdullah Rashed Alharbi
King Saud University, Kingdom of Saudi Arabia
E-mail:
dr_alharbi99@hotmail.com

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Abstract

Unclassifiable interstitial lung diseases represent about 15% of all patients with interstitial lung disease diagnoses. Hence, it represents a significant proportion of patients, which requires a specialized team to treat. Unlike other types of interstitial lung diseases, it is difficult to confirm the diagnosis of unclassified interstitial lung diseases except with the help of a multi disciplinary team due to the patients' heterogeneity. The present study was conducted with the aims to investigating the medical literature to assess the treatment strategies for unclassified interstitial lung diseases. The literature was examined through Medline, PubMed, Embase, and Ovid database in the duration from 2010 to 2020. Searching terms included were a combination of ''Management'' or ''Treatment'' and "unclassified interstitial lung diseases" or ''UILD'' and ''outcome''. Following this, results were refined to include only original research studies investigating the treatment strategies for unclassified interstitial lung diseases during the past decade. Selected trials mentioned the type of medication used as well as its outcome on treatment. A total of 589 studies were recovered. Following the exclusion of papers about animals and the inclusion of just human trials, 27 articles were found. Seven papers were found to be eligible, with a total of 1053 patients suffering from unidentified interstitial lung disorders. Four studies were double-blind, randomized controlled trials, with three of them multi-center. One study was retrospective, and two studies were case reports. The review concluded that pirfenidone (monotherapy or in combination) and nintedanib are the two most promising medications for unclassified interstitial lung diseases. More studies with a robust design are required to examine potential intravenous cyclophosphamide and immune therapy treatment.

Key words: Unclassified interstitial lung diseases; Management; Outcomes; Review

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Introduction

Interstitial lung disease (ILD) is categorized into multiple conditions that constitute fibrosis or inflammation of the lung parenchyma.[1] The etiology of ILD can be due to some factors; however, some cases are idiopathic.[2] Idiopathic ILD represents a challenge for clinicians due to its difficult diagnosis and treatment.[3]

In order to diagnose and classify ILD, a multi-disciplinary team is required, due to the systemic symptoms that may accompany respiratory symptoms of ILD.[4] However, many patients are challenging to diagnose and are given a diagnosis of unclassified ILD.[5] This case is typical, especially in some conditions such as chronic hypertensive pneumonitis, ILD, and fibrosis and connective tissue disease associated-ILD (CTD-ILD).[6]

Unclassifiable interstitial lung disease represents a heterogeneous condition, representing a group of undiagnosed fibrotic ILDs;[7] hence, patients with unclassified ILD will have the clinical manifestations of both interstitial pulmonary fibrosis and non-fibrotic ILD.[8] These common clinical manifestations include dry cough, dyspnea, and autoimmune disease.[9]

The treatment of unclassifiable ILD includes Pharmacological and non-pharmacological interventions.[10] The non-pharmacological interventions included vaccines, oxygen supplementation, smoking cessation, vaccinations, supplemental

oxygen, and pulmonary rehabilitation.[11] Also, medications can be used to treat unclassified interstitial lung disease. The last resort should be lung transplantation in resistant cases.[12]

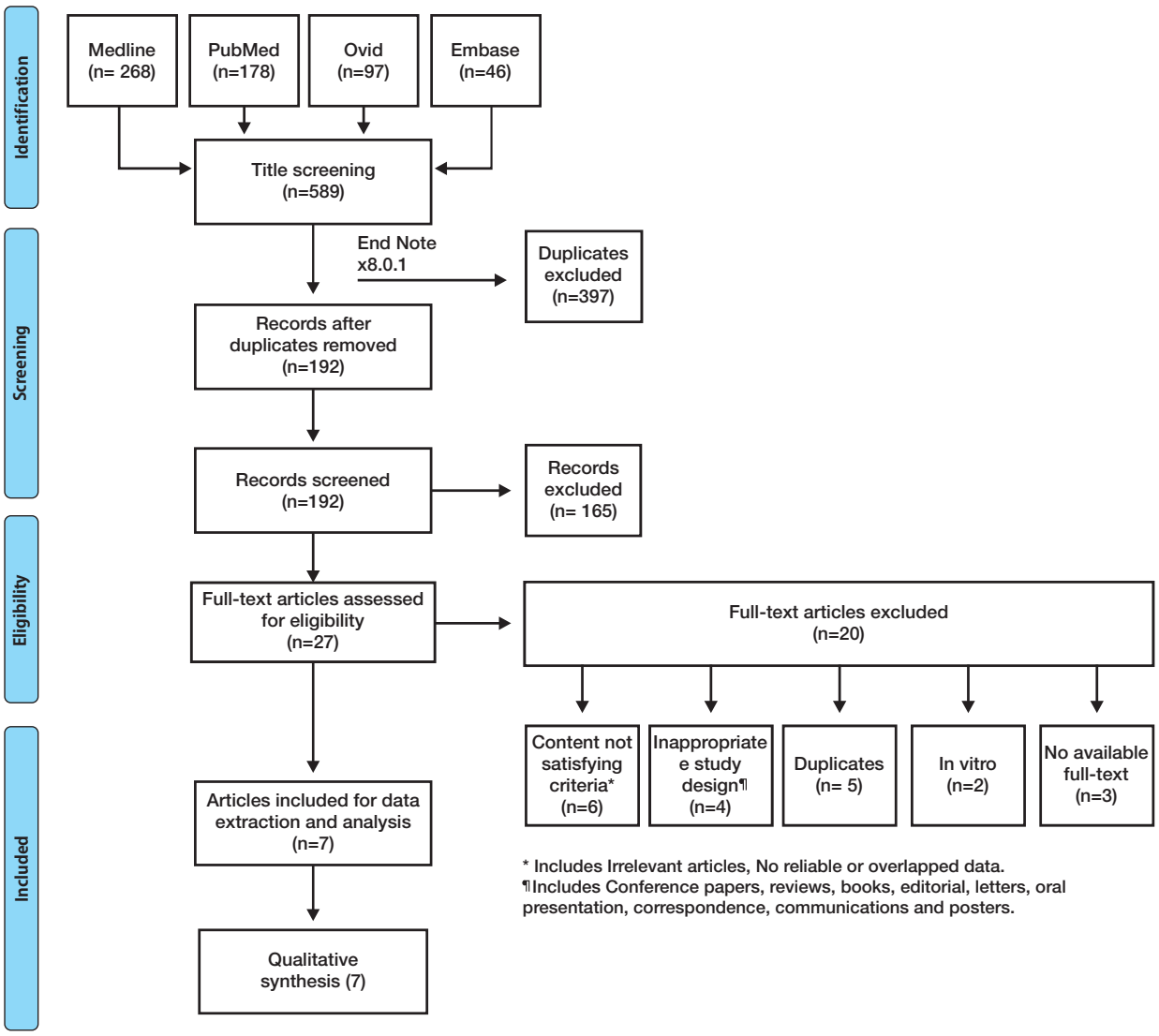
However, during recent years, there has been a debate over the medications used for the treatment of this challenging type of ILD.[13] As a result, the goal of this systematic review is to look at the literature over the last decade for management outcomes of unclassified interstitial lung disease.

Methodology

The PRISMA checklist instructions for systematic review and meta-analysis were followed for conducting this systematic review of the literature.[13] This systematic review was conducted by scanning four electronic databases, including Medline, Embase, Pubmed, and Ovid, for eligible studies from 2010 to June 2020.

Search Strategy

Searching terms included "Management" or "Treatment" and "unclassified interstitial lung diseases" or "UILD" and "outcome". To ensure that no suitable papers were missed, we meticulously evaluated all of the titles and abstracts that surfaced as a result of the primary search. The results were then filtered to include only original research publications published in the last decade that looked at treatment strategies for unclassified interstitial lung disorders. Moreover, the selected trials mentioned the type of medication used as well as its outcome on treatment. In addition, all study designs from various countries were incorporated. Only research published in English were designated as related studies, which can therefore be reviewed further in the next phase.



Eligibility Criteria

The inclusion criteria for selecting the studies that would be examined in the systematic review were defined after this stage. Abstracts were manually reviewed to determine which ones should be considered. The inclusion criteria were that there be enough information on the type of drug taken and the treatment outcome. Furthermore, only studies involving adult participants were included. In addition, the references of selected trials were examined to see whether there were any similar articles. Finally, the required data sets were acquired and summarised from the final list of qualifying papers. In vitro or animal involvement, overlapping or missing data, a lack of full-text journals, or an improper study design were all reasons for studies being rejected. Figure 1 shows the entire search process in detail.

Results

Total of 35 patients were included in our study from January 2016 to January 2019. All these patients had traumatic diaphragmatic hernia following blunt trauma, penetrating trauma and congenital diaphragmatic hernia were excluded. Out of these 35 patients 24 patients presented to emergency department, 07 patients presented late to our OPD with history of trauma and four patients who were admitted in other units post trauma and were shifted to our ward.The age range in our study was from 07 years to 62 years. Most of the patients were in the age group of 18-48 years (68.9%)

There were 24 (68.57%) male patients in our study and 11 (31.41%) female patients.

Thirty-one patients (88.57%) presented with left sided traumatic diaphragmatic hernia, while 4 patients (11.42%) presented with right sided traumatic diaphragmatic hernia. Most common presenting symptoms in these patients were chest and abdominal pain in 27 (77%) of the patients, followed by shortness of breath in 19 (54%) and vomiting in 10 (28.6%). On physical examination, air entry was decreased in 28 (80%) patients and bowel sounds were heard in the chest in 13 (37%). The patients who presented had different mechanism of injuries 21

Author(s)	Year	Study Design	Sample Size	Type of treatment	Objective	Result
Wells et al.[15]	2020	A multi-center RCT, double-blind	114	Nintedanib	To explore the safety and efficacy of nintedanib in patients with unclassified ILD.	Nintedanib can decrease the rate of progression of unclassified ILD, in terms of improvement of forced volume capacity (FVC) and chronic fibrosis (p value <0.001).
Martinez et al.[16]	2020	RCT, double-blind	663	Nintedanib	To assess the long-term safety of nintedanib in patients with unclassified ILD.	Adverse events leading to discontinuation of the drug occurred in 19.6% of patients treated with nintedanib, compared with 10.3% of patients treated with placebo (p value= 0.024). Diarrhea was the most frequent adverse event and the most common cause of discontinuation of treatment.
Kreuter et al.[17]	2020	A multi-center RCT, double-blind	127	Pirfenidone	To discuss a subgroup analysis for patients with unclassified ILD who had a Concomitant Mycophenolate Mofetil	Despite the overall finding of the trial proposed that pirfenidone is effective in progressive fibrosing unclassified ILD patients, this combination with MMF appears to propose a differential outcome of pirfenidone on FVC change (assessed through spirometry). The safety profile of pirfenidone was similar regardless of the MMF treatment combination. Further studies are required to explore these findings in a larger group of patients.

Maher et al.[18]	2019	multi-center RCT, double-blind	127 on pirfenidone, 126 on placebo	Pirfenidone	To explore the safety and efficacy of pirfenidone (2403 g/day) compared to placebo over six months in progressive fibrotic unclassified ILD.	Pirfenidone is effective in patients with progressive fibrotic unclassified ILD over six months, with proper safety and tolerability. However, further clinical investigation of pirfenidone in patients with fibrosing unclassified ILD is required. Further analyses are required before daily home spirometry can be used as a primary outcome measure. Patients with unclassified ILD are considered a heterogeneous patient population; hence, treatment should be individualized.
Wiertz et al.[19]	2018	multi-center RCT, double-blind	20	intravenous cyclophosphamide pulse therapy (ICPT)	To explore the outcomes of 6 months ICPT in corticosteroid refractory unclassifiable interstitial lung pneumonia (uILP) patients.	All patients were refractory to corticosteroids before the start of ICPT. In unclassifiable IIP patients, the effect of treatment was less clear and suggested a reduction in the disease rate. A nonsignificant reduction of FVC reduction was noted. Six months following the initiation of ICPT (FVC declined from 18.2% before to 5.9%, p=0.241). In 13 unclassifiable ILP patients at 12 months, sustained improvement of FVC after ICPT was identified in all unclassifiable IIP patients. However, consolidation therapy consi-sted of many medications, such as corticosteroids, azathioprine, MMF, and rituximab. Steroid refractory unclassifiable IIP patients treated with ICPT showed a significant improvement in FVC.
Koga et al.[20]	2018	Case report	1	Intensive immunotherapy	To describe the use of an anti-MDA-5 antibody in a patient with unclassified interstitial pneumonia.	Intravenous cyclophosphamide [IVCY; 840 mg (500 mg/mm2)] and tacrolimus therapy repeated every two weeks and increased to IVCY dosage to 900 mg. High-dose intravenous immunoglobulin was also given. After the fourth cycle (each cycle every two weeks) of intravenous cyclophosphamide (IVCY) therapy, hypoxia began to improve, and the serum levels of ferritin were decreased to 767 ng/mL after two months of hospitalization. High-dose

Yokohori et al.21	2017	Case report	1	Pirfenidone and Erythromycin combination		steroid therapy did not improve uILD. The administration of intensive immunosuppressive therapy, including high-dose corticosteroids, an oral calcineurin inhibitor, and IVCY, before the onset of irreversible pulmonary changes, might result in an improved prognosis
					To investigate the efficacy of combined therapy with pirfenidone at 1,200 mg/day Furthermore, erythr *omycin at 400 mg/day in bronchioloalveolar disorder (HABA) associated unclassifiable inter stitial pneumonia.	The administration of erythromycin improved HABA associated interstitial pneumonia. The dyspnoea on exertion, the oxygen saturation, and pulmonary functions did not progress; though, the CT findings of Broncho vascular bundle-dominant reticular shadows and GGO had deteriorated six months after the start of the pirfenidone treatment. This combined therapy has been continued for more than two years, with no progression of dyspnoea on exertion or abnormalities on chest CT.

(60%) patients had road traffic accident, 7 (20%) had history of fall, 6 (17%) patients had fall of heavy object or roof over them and one patient presented with crush injury between two objects. Chest x-ray was performed in all patients and was diagnostic in 27 (77%). Similarly all the patients underwent ultrasonography which was found to be positive in 30 (85.72%) patients at presentation. CT-Scan and fluoroscopy was performed in difficult cases and there diagnostic accuracy was (100%).

Common associated injuries in traumatic diaphragmatic hernia in our study group were, rib fracture in 12 (34.2%) followed by limb injuries 9 (25.71%) splenic injury in 6 (17%), liver injuries 4 (11.4%), head injury in 5 (14%) and pelvic fracture 01 (2.85%) (Table 1).

Discussion

Unclassified interstitial lung diseases are a group of heterogeneous conditions that represent a challenge in their diagnosis and treatment.[8] Patients with uILD, usually have other symptoms, including respiratory symptoms, which requires the co-operation of a multidisciplinary team.[19] Due to the difficulty of identifying patients with UILD, there is not enough data on the treatment outcomes of these patients and the medications used to treat UILD.[16]

The present review investigated the safety and efficacy of the medications used in the treatment of UILD, through reviewing the medical literature in the past decade.

Different medications have been examined in this review. The use of nintedanib for the treatment of UILD has been examined in two studies. Wells et al.[15] examined the safety and efficacy of nintedanib in patients with UILD. Wells et al.[15] showed that nintedanib could significantly reduce the progression of UILD through an improvement in FVC and chronic fibrosis (p value<0.001).

However, Martinez et al.[16] examined the safety of nintedanib on a long term basis in a double-blind, randomized controlled trial. Martinez et al.[16] showed that the discontinuation rate of nintedanib was significantly higher in the nintedanib compared to the control group, where diarrhea reported as the most frequent cause of drug discontinuation.

Pirfenidone was also investigated in three studies, as a monotherapy or combination therapy. As a monotherapy, Maher et al.[18] examined the safety and efficacy of pirfenidone treatment over six months. Maher et al.[18] demonstrated that pirfenidone monotherapy had an acceptable safety and tolerability as well as high efficacy over six months, in patients with progressive fib rotic UILD.

As a combination therapy, Kreuter et al.[17] examined the treatment outcomes of pirfenidone in patients already on Mycophenolate mofetil (MMF). Kreuter et al.[17] revealed that the combination did not significantly

differ from monotherapy in terms of safety; however, the efficacy outcome was controversial.

Another case report by Yokohori et al.[21] described the efficacy of pirfenidone and erythromycin combination in a case report for a patient with the bronchioloalveolar disorder (HABA)-associated UILD. Yokohori et al.[21] showed that the combination improved patient's symptoms, including dyspnoea on exertion and pulmonary functions even after continuation for two years.

Another treatment option was intravenous cyclophosphamide pulse therapy (ICPT) tested by Wiertz et al.,[19] who included patients refractory to corticosteroid treatment for unclassifiable interstitial lung pneumonia (UILP). Wiertz et al.[19] suggested a reduction in the disease progression, with sustained improvement after the administration of ICPT.

The use of intensive immunotherapy was also described in one case report by Koga et al.[20] using anti-MDA-5 antibody with intravenous cyclophosphamide, corticosteroids, and oral calcineurin inhibitor in a patient who had unclassifiable interstitial lung pneumonia (UILP). Koga et al.[20] showed that early administration of the described combination, before irreversible lung damage, can lead to improved prognosis in patients with UILP.[20]

Despite the scarcity of data in the medical literature on the treatment of uILD, the present systematic review included studies with robust study design (four studies were double-blind, randomized controlled studies), which strengthens the outcomes of the present review and encourage further studies on the treatment of UILD.

Also, it should be noted that in the past three years, there has been significant attention to the management of UILD, with an increasing number of well-designed recently on the disease, which an interest in the medical community to address the gaps in the literature for UILD. This is considered the first systematic review to evaluate the treatment outcomes of UILD.

Conclusion

Different medications have been examined in the past recent years for the treatment of UILD. The most promising medications are pirfenidone and nintedanib. Nevertheless, the use of intravenous cyclophosphamide pulse therapy and immune therapy represent potential medications that require further studies to investigate, with more robust study designs. The safety of UILD medication is generally acceptable, except for an increased incidence of drug discontinuation due to the presence of diarrhea with nintedanib.

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