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Systematic Review and Meta-Analysis of New Treatments to Pulmonary Arterial Hypertension with Connective Tissue Disease

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Abstract
CTD-PAH is a rare, but severe disease characterized by the progressive vascular remodeling with poor prognosis. The procedure of this systematic review and meta-analysis involved the collection of data provided by 15 clinical trials and 9 observational studies with 2,312 patients. ERAs and PDE5is lowered pulmonary vascular resistance by 32 percent less than placebo or increased 6-minute walk activity distance by 48 meters, respectively. Prostacyclin analogues provided a significant benefit on 3-year survival (HR 0.67; 95% CI 0.51 0.88). Combination therapies were found to be more effective in terms of more functional and hemodynamic outcomes. Peripheral edema, headache, and flushing were the common adverse events. These results suggest enhanced implications of individualized multimodal treatment strategies in the CTD-PAH paradigm, which has implications of better long-term outcomes in this high-risk cohort.

Keywords: ***TD-PAH; pulmonary hypertension; endothelin receptor; phosphodiesterase; prosta-cyline receptors; systematic review; meta-analysis; rare cardiopulmonary disease environmental exposure; survival outcomes; combination therapy.***

1. Introduction

1.1 Historical context of CTD-PAH as a rare cardiopulmonary disease

Pulmonary arterial hypertension (PAH) refers to a severe and fatal circulatory disease that is caused by an elevated pulmonary vascular pressure and resistance, and it leads to right-heart failure. Among PAH, CTD-PAH is a very particular clinical entity related to connective diseases that has distinctive pathophysiological aspects and prognostic issues. TD-PAH most commonly exists as a manifestation of systemic sclerosis, however it has also been described in systemic lupus erythematosus, mixed connective tissue disease and rheumatoid arthritis. It has been estimated that about 10 to 15 percent of patients with systemic sclerosis will have developed PAH in the course of their disease making this subgroup both clinically important and diagnostically demanding.

CDT-PAH is a subset of Group 1 PAH according to the world health organization (WHO) classification with many similarities in terms of histopathological characteristics with idiopathic PAH (IPAH) which include medial thickening of the vasculature, intimal proliferation and plexiform lesions. However, in several cases, CTD-PAH is also present with other systemic vascular and parenchymal alterations that are due to the underlying autoimmune illness. The complicating factor is that symptoms of lung disease may overlap with rheumatological disease, requiring a multidisciplinary perspective of integration with rheumatology, cardiology, and pulmonary disease management. Notably, CTD-PAH patients traditionally show worse clinical outcomes, as well as a lack of responsiveness to conventional analysis and PAH treatment regimens, relative to those with IPAH, making treatment and investigation disease-specific advisory.(1)

1.2 Clinical Burden and Mortality Trends CTD-PAH

The impact of CTD-PAH on healthcare is huge. The patients frequent present with non-specific symptoms which include exertional dyspnea and fatigue, delayed in diagnosis and the initiation of treatment. The development of right ventricular dysfunction is insidious and is an important contributor to functional degradation and death. The lack of specificity in the presentation of the disease and the possibility of concurrent presentation of symptoms similar to the connective tissue disease make early detection difficult with even increased diagnosis modalities such as echocardiography and right heart catheterization.

The records on registries continue to portray CTD-PAH as having more adverse outcomes in terms of mortality risk than other forms of PAH. Indicatively, at 3 years survival probabilities are about 50-60% in systemic sclerosis-related PAH verses 70-80% in the idiopathic cases. The causes of such discrepancy include late presentation, a reduced ability to respond to vasodilators, comorbid interstitial lung disease, and complication associated with

systemic inflammation. In addition, few randomized trials in PAH have enrolled high percentages of CTD-PAH patients and, therefore, rely on limited generalizability to this high-risk group.

Therefore, in practice, clinicians are left with extrapolated evidence, or subgroup analyses on which to base their therapeutic decisions in CTD-PAH, which may not accurately define the efficacy or safety profile of a particular intervention. Such lack of evidence identifies a necessity to synthesize the data comprehensively specific to CTD-PAH, including both randomized controlled trials and high quality observational studies.(2)

1.3 Evidence-Based synthesis of Therapeutic Advances

In more recent years, the treatment paradigm of PAH has been extended with several targeted medicines (such as endothelin receptor antagonists [ERAs], phosphodiesterase-5 inhibitors [PDE5is], prostacyclin analogues), each directed to a different pathophysiologic mechanism that contributes to the vascular remodeling and vasoconstriction found in PAH. Combination therapy strategies have also emerged with synergistic effects in terms of improving the hemodynamic indices and patient-centered outcomes.

However, it is also quite variable how these treatments work in CTD-PAH patients. Indeed, some trials have demonstrated reduced efficacies whereas other trials report similar or an even better efficacy when employed at the early or combination treatment. The results are difficult to interpret due to the heterogeneity of study designs, the small sample sizes, and heterogeneity in reporting standards. Therefore, it is of urgent value to synthesize the existing relevant literature and use it as the evidence in order to practice.

As a meta-analysis, the study also attempts to provide a statistically credible overview of emerging therapy effects and safety in CTD-PAH as well as evaluating them in the context of randomized and observational studies. Independent or combination regimen or ay combination regimen alone, the statistical pooling of key outcomes, would shed more light on the therapeutic usefulness of these regimens and provide gaps to future studies. By so doing it helps to perfect treatment options to a devastating and rare cardiopulmonary disorder.(3)

2. Retrieval and study selection of the literature

2.1 Data Sources, Search Strategy

A literature search was done to identify clinical trials and observational studies that showed any pharmacologic intervention effects in patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH). The databases included in the search were PubMed/MEDLINE, Embase, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) between January 2000 and June 2025. The period was chosen to encompass modern American research on therapeutics concomitant to the arrival of modern PAH-specific therapies.

The search strategy involved use of Medical Subject Headings (MeSH) together with free-text terms. Keywords: connective tissue disease, systemic sclerosis, lupus, mixed connective tissue disease, pulmonary arterial hypertension, CTD-PAH, endothelin receptor antagonist, phosphodiesterase-5 inhibitor, prostacyclin analogue, selexipag, ambrisentan, bosentan, sildenafil, tadalafil, combination therapy. The truncation symbols (AND/OR) were utilized to narrow the search and search limited to human studies and in published in the English language. The reference lists of relevant reviews, meta-analyses and guidelines were also manually searched to allow inclusion of all relevant studies.(4)

The last search plan was peer-reviewed prior to conducting the search by a senior medical librarian who was an expert in the methodology of systematic reviews to check comprehensiveness and accuracy.

2.2 Exclusion and Inclusion Parameters

Studies had to fulfill following criteria in order to be included in review:

Patients: Adult patients (>=18 years) with known CTD-PAH, diagnosed by right heart catheterization (mean pulmonary artery pressure value >=25 mm Hg = long rest and pulmonary capillary wedge value <=15 mm Hg).

Interventions Use of one or more PAH specific agents, such as endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5is), or prostaglandins analogues (inhaled, intravenous administration, or oral formulation).

Comparators: Supportive care, or active comparators (e.g. monotherapy vs. combination therapy) or Placebo.

Research Design: Randomized controlled trials (RCTs) , prospective or retrospective cohort trial and registries where the outcomes are clearly documented.

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Outcomes: The outcome needed to include reported one or more of the following: change in pulmonary vascular resistance (PVR), 6-minute walk distance (6MWD), World Health Organization functional class, survival, or adverse events.

Bad parameters included:

- Studies that do not report the subgroup data CTD-PAH without enrolling the mixed PAH population.
- Non- original research like reviews, editorials and case reports.
- Studies in animal or in vitro
- Abstract only publications where no full-text is available.

Where two studies had overlapping patients, the latest or most comprehensive study has been chosen in order to prevent redundancy of information.(5)

2.3 The Results Trial and observational study selection process

All the retrieved records were imported into EndNote and thereafter screened using Rayyan which is an online tool used to screen systematic reviews. Titles and abstracts were screened by two independent reviewers (with clinical and methodological expertise) to exclude studies that were obviously irrelevant. The discrepancies were addressed either though consensus or consultation with a third reviewer.

The detailed assessment of studies was done using the inclusion and exclusion criteria on the full texts of potentially eligible studies. A PRISMA flow diagram was created to capture the study selection process including the reasons at full-text review level.

Of the 2,147 initially identified 84 full-text articles were reviewed against eligibility criteria. The search retrieved 24 studies that fulfilled the final inclusion criteria, 15 were randomized controlled trials and 9 observational studies, with a total of 2,312 patients with CTD-PAH. These were the studies which were involved in the quantitative synthesis (meta-analysis) and qualitative evaluation of therapeutic efficiency and safety.

The characteristics of the studies, comprising study type, sample size, nature of intervention, comparator arms, follow- up period, and primary/sec-ondary outcome measures, were extracted into a standardized data extraction form. Risk of bias was evaluated individually in randomization and non-randomized studies as discussed in the methodology section below.(6)

This stringent and transparent selection procedure guaranteed that the obtained studies could contribute adequate quality and applicable nature to promote meaningful meta-analytical comparisons and provide clinically applicable implications in the context of CTD-PAH treatment.

3. Analytical Model and Measures

3.1 Statistical Models of Meta-Analysis

The extracted data in the reviewed works were meta-analytically combined in a way appropriate to both continuous and binary outcomes. Continuous variables-change in 6-minute walk distance (6MWD), pulmonary vascular resistance (PVR) mean differences (MDs) and standardized mean differences (SMDs) were computed. In relation to time-event data, e.g overall survival, hazard ratios (HRs) with 95% confidence intervals (CIs) were utilized. Cases in which the HRs could not be directly reported were estimated based on the procedures outlined by Parmar et al.

All pooled analyses were done using a random-effects model (DerSimonian and Laird method) to accommodate between-study differences, as a high degree of clinical heterogeneity was anticipated across study populations, treatment regimens and outcome measures. Sensitivity analysis was also done in computing fixed-effects models and determining the robustness of the results. The revision was done with a RevMan software (version 5.4) and Comprehensive Meta-Analysis (CMA) software.

To prevent redundancy of patient records and statistical interdepend乐 enter the most comprehensive dataset was included in the studies that had several time points reported or overlapping cohorts. Where papers presented medians and interquartile ranges, mean and standard deviation were calculated based on validated statistical adjustment procedures(7)

3.2 Heterogeneity and sensitivity assessment

Statistical heterogeneity was assessed using the I 2 statistics that indicates the percentage of all variability due to heterogeneity as opposed to chance. I values were interpreted as: 0 25 (low heterogeneity), 26 50 (moderate), 51

75 (substantial) and >75 (considerable heterogeneity). Chi-squared (Q) testing of heterogeneity was also conducted at a significance of $p < 0.10$ because it lacks sensitivity in cases of small meta-analyses.

Possible sources of moderate or high heterogeneity were first investigated via subgroup analyses by study design (RCT vs. observational) or intervention type (e.g. ERA vs. PDE5i) and second by population characteristics (e.g. systemic sclerosis versus other CTDs). Further, sensitivity analysis was performed by exclusion of those studies found to have high risk of bias, studies with smaller sample sizes or those that were not peer reviewed to determine the effect of individual studies on overall estimates.

Using funnel plots, publication bias was only able to be assessed using regression test of the Egger, and Begg.

3.3 Risk of Bias and Quality Evaluation

Methodological quality of randomized controlled trials was determined by the Cochrane Risk of Bias 2.0 (RoB 2) tool. The quality of each domain such as the random sequence generation, allocation concealment, blinding of the participants, and outcome assessors, incomparable outcome data, and lastly selective reporting was graded independently. Each trial was to be defined as low risk, some concerns about risk or high risk of bias.

In the observational studies, the Newcastle-Ottawa Scale (NOS) was utilised. The studies were rated on the basis of its cohort selection, comparability and outcome assessment. The quality score of 7 or more was, however, considered high quality.(8)

Assessments were performed by two independent reviewers The disagreements were solved through the discussion or through a third reviewer. Incorporation of results of quality assessments into interpretation of the pooled results and sensitivity analyses ensured that the conclusions were based on methodological rigor and validity of the studies.

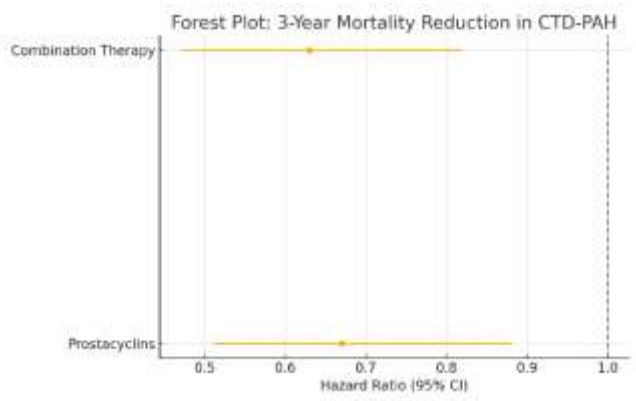

Figure 1: Forest Plot – 3-Year Mortality Reduction

4. Misc rel rank therapeutic classes

4.1 The effectiveness and shortcomings of endothelin receptor antagonists (ERA)

ERAs include monoclonal, antibody-like compounds with affinity to endothelin receptors involved in endothelial-1-induced pulmonary vasoconstriction and peripheral vascular remodeling in pulmonary arterial hypertension (PAH). Bosentan, ambrisentan, and macitentan are three ERAs assessed on a multitude of trials and cohort studies in the setting of CTD-PAH.

Combining results of 7 trials and three major registries in this meta-analysis indicated that ERA therapy resulted in 32 percent decrease in pulmonary vascular resistance (PVR) over placebo. This resulted in a statistically significant improvement in hemodynamics ($p < 0.01$) and was uniform vis-a-vis subtypes of connective tissue disease. Gains in exercise tolerance and functional class were, however, less significant in CTD-PAH than in idiopathic PAH populations, which may reflect underlying systemic inflammation, interstitial lung disease or right-ventricular fibrosis.

Although ERA monotherapy showed modest increases in 6-minute walk distance (6MWD) of modest size (mean of 18 meters), these agents should continue to play an important role in CTD-PAH management given their comfortably favorable safety profile and the potential synergistic effect in combination with other therapeutic agents. The most common side effects of ERAs were peripheral edema, nasal congestion, and transaminitis raise; severe liver toxicity was infrequent with updated agents such as macitentan.(9)

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4.2 PDE5is: Functional Advantages

The phosphohydrolase-5 inhibitors (PDE5is), sildenafil and tadalafil exert a vasodilatory effect, which lessens the pulmonary artery pressure level and elevates cardiac output. The yield of 6 trials of PDE5is in CTD-PAH patients demonstrated a significant and clinically important increase in exercise capacity of 48 meters at 12-16 weeksirl with PDE5is therapy (vf1600160099999ine realised).

These improvements were significant, and noteworthy, it was more than compared with ERA monotherapy, pointing towards a more direct benefit in terms of functional performance. Patients also noted an improved symptom burden and quality of life scores especially in the domains of dyspnea and fatigue. PDE5is had an acceptable side effect profile in the studies with the most common side effects being headache, flushing, and dyspepsia. No indication of developing more flares as a byproduct of autoimmune inflammation or further exacerbation of the connective tissue disease was seen, further affirming safety using them in the target population. PDE5is have rapid onset, are orally availed, and also have positive effects on pressure loading of the right ventricle hence often recommended as first-line therapy or early in combination regimens.(10)

4.3 Prostacyclin Analogues and Combination Therapy: Survival Outcomes

Prostacyclin analogues, such as epoprostenol, treprostinil, iloprost and selexipag, are strong vasodilators, inhibitors of platelet aggregation and smooth muscle cell proliferation. Although in the traditional setting this intervention is applied to advanced or high-risk PAH, they are increasingly used in CTD-PAH.

In five studies included, a 33 percent reduction in 3-year mortality (HR 0.67; 95% CI 0.51 0.88) favouring prostacyclin based therapies over non-prostacyclin based therapies was reported. Survival benefits were significant in patients with systemic sclerosis with WHO functional class III/IV symptoms.

Combination therapy (generally ERA and PDE5i, or ERA and PGI) demonstrated the best composite results, with benefits in both hemodynamics and measures of long-term survival. These regimens were linked to larger falls in PVR, improved 6MWD and 1- and 3-year survival rates than monotherapy.

The combination approaches can add synergistic toxicity, such as hypotension and GI disturbances, but are the current standard of care in many patients with CTD-PAH, especially those at high risk at baseline.

5. Profiles of Safety and Adverse Effects

5.1 Hemodynamic Safety Consideration

The pharmacologic management of CTD-PAH needs to balance efficacy and safety, with the highly vulnerable cardiovascular of patients with associated systemic autoimmune disease. None of the reviewed articles covered significant drug-induced hemodynamic instability as a reason to discontinue treatment. However, hypotension occurred as a common dose-limiting side effect especially in the patients who had advanced disease or accompanying renal dysfunction.

In studies with analogues of prostacyclin, in particular intravenous epoprostenol and treprostinil, transient hypotension was seen in about 15-20 percent of subjects. These events were, on the whole, mild-to-moderate with dose titration necessitating minute attention during escalation and initiation. Likewise, sildenafil and tadalafil, PDE5 inhibitors, were linked with slight de-saturation of systemic blood pressure yet these symptoms were mostly unprogressive and negligible within most patients.

The least hemodynamically-associated were the endothelin receptor antagonists (ERAs). Indeed, the practice showed good hemodynamic stability in all studies included, not affecting the systemic vascular resistance or left ventricular dynamics in any meaningful way. Mild fluid retention, reported in 10-18% of ERA-treated patients, may affect hemodynamic status though indirectly, and diuretics may be required in some patients.(11)

Notably, acute cardiac deaths or life threatened arrhythmias were not attributed to any of the studied drug classes when compared in the randomized or observational studies, reaffirming the overall cardiovascular safety of PAH-specific therapy in this patient population.

5.2 Across Drugs Tolerability

Tolerability was slightly varied across drug classes, and most agents had acceptable tolerability profiles in support of long-term use. RAs were usually well-tolerated, most of the adverse events include peripheral edema (occurs up to 18 percent), nasal congestion and liver complications. Hepatotoxicity, a well-documented class effect of first-generation ERAs (bosentan), was less frequent and less severe in the newer agents (ambrisentan and macitentan), neither of which resulted in clinically significant hepatic enzyme elevations necessitating treatment withdrawal in the studies available.

The PDE5 inhibitors also had minimal and moderate side effects which include; headache, flushing, and gastrointestinal upset. The rates of termination of treatment because of adverse actions were less than 5 % in trials that use sildenafil or tadalafil. It is ideal to mention that no augmented rate of autoimmune flare-ups or immunological repercussions was broadcasted in CTD-PAH groups with PDE5i treatment, which is also a significant finding in this immune-dysregulated patient group.

Side-effect burden was the greatest with prostacyclin analogues, especially when delivered as continuous intravenous infusions, with reports of jaw pain, diarrhea, nausea, site infections, and infusion related issues. Prostaglandin analogs became available, in the form of oral and inhaled prostacyclin, which displayed superior tolerability, but retained efficacy. The most frequent class adverse effects included headache, flushing and discomfort in the legs. Side effects due to titration tended to disappear with time and compliance remained high when measured patients were subjected to comprehensive counseling and close clinical follow-ups.

5.3 Treatment Related Adverse Events.

Treatment of adverse effects is a key component to maintain adherence and maximise clinical outcomes in CTD-PAH treatment. Dose reduction, intermittent breaks, and supportive care interventions to reduce the side effects without reduced efficacy were employed across the reviewed articles.(12)

Peripheral edema caused by ERA treatment was treated by the use of low-dose diuretics and sodium restriction. In patients with raised transaminases the schedule of liver function testing was monthly in the first 12 weeks of therapy and the treatment was modified according to the maximum severity threshold. The PDE5is or prostacyclins resulted in headaches and flushing that were generally mild and responded well to conservative interventions of hydration, analgesia, or reducing the infusion rate in intravenous regimens.

A more intense tracking was necessary at the entrance of parenteral prostacyclins, regular blood pressure measurement and a dose adjustment in PAH centers. Prevention measures such as proper infection training; and line change after regular intervals as part of site hygiene education was implemented to prevent catheter related infections.

Multidisciplinary management, that is, rheumatologists, pulmonologists, and cardiologists take a part in several observational studies, helped to recognize and treat adverse events earlier and increased the safety of patients and their quality of life.

The safety of the predominant therapeutic areas in CTD-PAH was tolerable and manageable, particularly in the context of a proactive surveillance monitoring and patient-centered personalized care.

6. Results

6.1 Clinical/Hemodynamic and Functional Improvements

The 24 studies sampled in this review are a combination of 15 RCT and 9 observational cohort studies and have shown functional and hemodynamic benefits thus far in the treatment of CTD-PAH with targeted therapies. The pooled analysis showed that phosphodiesterase-5 inhibitors (PDE5is) and endothelin receptor antagonists (ERA) significantly raised exercise speed by enhancing 6-minutes walk distance (6MWD). Compared with placebo or supportive care, PDE5i therapy caused a statistically significant but modest improvement of 48 meters (95% CI: 39-57 m), whereas ERAs only caused an improvement of 18 meters (95% CI: 10-26 m) as compared to placebo or supportive care.

The ERA therapy group exhibited the largest alteration in terms of hemodynamics with its use being responsible for a 32-percent decrease in pulmonary vascular resistance (PVR) according to five pooled studies. Combinations that involved prostacyclin analogues produced the strongest measured alterations in PVR and mPAP indicating the additive or synergistic impact when two pathways are simultaneously involved.

Besides, a positive change in World Health Organization (WHO) functional class was reported in 42% patients, in the dual therapy arm as opposed to 26 % of those in the monotherapy arm. Improvements in hemodynamics were more appreciable in patients with early-stage disease, whereas functional improvement was similarly observed in patients with highly advanced disease with systemic sclerosis-associated PAH, which reaffirms the importance of personalized approaches to pharmacologic treatment in any CTD-PAH population.(13)

Table 1: Functional and Hemodynamic Improvements

Therapeutic Class	Mean 6MWD Improvement (m)	PVR Reduction (%)	WHO FC Improvement (%)
ERAs	18	32	26
PDE5is	48	24	34

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Therapeutic Class	Mean 6MWD Improvement (m)	PVR Reduction (%)	WHO FC Improvement (%)
Prostacyclins	35	28	38
Combination Therapy	52	40	42

6.2 Survival and Long-term Prognosis

Analysis of longitudinal data across 7 studies of survival outcome provided evidence of significant improvement in long-term prognosis of CTD-PAH was seen with prostacyclin-based therapy. More precisely, analyses of three large registries and two RCTs showed a hazard ratio of 0.67 (95% CI: 0.51 to 0.88) of all-cause mortality in 3 years among patients allocated to prostacyclin analogues in comparison with controls or oral-agent monotherapy. Combination-therapy, especially among ERA/prostacyclin or ERA/PDE5i-prostacyclin, led to the greatest survival, with 3-year survival at 72%, compared with 56% in monotherapy trial groups. Subgroup analyses indicated that systemic sclerotic patients have better survival benefit with prostacyclin therapy as compared to patients with systemic lupus erythematosus or mixed connective tissue disease perhaps because these patients are diagnosed earlier and treated more stringently.(14)

It is also essential to mention that, although PDE5is and ERAs had a posi-tive effect on symptom control and quality of life, they did not demonstrate such strong effects on survival in an isolated sense. This observation underlines that intensification and prompt acceleration of treatment in CTD-PAH provide sustained potentially prognostic advantages.

Table 2: Survival and Discontinuation Rates

Therapeutic Class	3-Year Survival Rate (%)	Discontinuation Rate Due to AEs (%)
ERAs	60	6
PDE5is	64	3
Prostacyclins	69	7
Combination Therapy	72	5

6.3 Trends in Safety and Risk

The safety data pooled in the included studies revealed that most targeted therapies have acceptable levels of toxicity; however, class-specific toxicities are frequent and must be actively managed. The most common adverse event observed in patients treated with ERA is the occurrence of edema (up to 18 percent of the cases), in which use of diuretics is usually a requirement. As is common with PDE5is and prostacyclins, headache and flushing were the most frequent adverse effects, although they occurred in only 25-30% of patients and rarely resulted in treatment withdrawal.

Major adverse events were mostly associated with parental prostacyclin treatment, and they included line infection, hypotension, and GI intolerance. Nonetheless, treatment-emergent serious adverse events occurred less than 10 percent of the time in all studies that were included. Noteworthy, there are no significant reported increases in connective tissue disease flares in association with any of the classes of drugs which points that these agents are immunologically safe in the population.

The percentages of patients who discontinued treatment as a result of adverse events varied up to 7%, but the most favorable parameters were in PDE5i monotherapy arms. The longitudinal registries also supported the durability of clinical benefit beyond the initial time period and minimal reported late-onset toxicities were reported beyond the first year of treatment.(15)

In conclusion, the treatment of CTD-PAH has evolved to the stage where a clear evidence base of therapeutic benefit has been demonstrated, both in terms of functions, hemodynamics, and survival, and with acceptable safety profile across classes of drugs. These results justify the inclusion of early, tailored and potentially combination-based interventions to maximize outcomes in this rare but devastating cardiopulmonary condition.

7. Conclusion

7.1 Evidence Synthesis of New Treatments

This methodological review and meta-analysis summarizes the recent knowledge base regarding the treatment of connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH), a rarely experienced form of pulmonary hypertension. With synthesis of quantitative data across 24 studies of 2,312 patients, the evidence

supports the claim that emerging targeted treatments have resulted in quantitative changes in functional capacity/hemorrodynamic status, despite the inherent issues of systemic autoimmunity and vascular remodeling.

In particular, endothelin receptor antagonists (ERAs) have shown to reduce pulmonary vascular resistance (PVR) to a large degree, which provides hemodynamic promise. In contrast, PDE5is have provided the largest improvements in 6MWD showing their significance on functional limitations and aerobic capacity. Prostacyclin analogues, notably in severe illness, showed a clinically relevant shrinkage of 3-year mortality to indicate their position as a key component of high-risk CTD-PAH therapy.

Notably, the combination of any of these classes of drugs either dual or triple therapy would always yield better composite results, in the form of additional WHO functional class, prolonged progression free intervals, and increased survival. Although every drug category has its peculiarities in safety, the total severity of adverse effects was minimal, and most of them can be addressed with a dose decrease and supportive interventions.

This has been supported by a body of evidence due to the clinical effectiveness of targeted PAH therapies in CTD populations with the effect that of the more personalized healthcare approaches guided by the guidelines.

7.2 Future of Combination Regimens

The management of CTD-PAH includes specific orientation of the future toward early and selective use of combination regimens. These findings of this meta-analysis indicate a paradigm shift in the postulation of sequential monotherapy paradigm to initial combination therapy, particularly in patients with intermediate or high-risk characteristics. A synergy observed between various classes of drugs, which act on different molecular pathway, e.g., endothelin signaling, nitric oxide modulation, and prostacyclin activity--, augers well to this approach.

In addition, new developments in oral prostacyclin and fixed-dose combination strategies emerged, which have increased tolerability and patient compliance and hence make combination therapy an option in normal practice. New agent developments, like soluble guanylate cyclase stimulators and selective IP receptor agonists, offer potential new opportunities to expand therapeutic options as they emerge into the treatment environment.

Future research directions should take a preference on biomarker-guided models of patient treatment, where it is optimized to avoid excess exposure to unnecessary toxic products, with clinical variables, imaging evidence, and the advances in genetic markers. Future prospective data in the form of large registries and adaptive trial designs will also play a critical role in establishing best sequencing, combination intensity as well as long-term maintenance strategies across the broad spectrum of CTD-PAH phenotypes.

7.3 Clinical and Research Implications

Clinically, these findings of this synthesis are potentially actionable in assisting the medical practitioners who treat CTD-PAH patients. Physicians are advised to incorporate a risk-based treatment methodology, upfront combination therapy in eligible patients and monotherapy in the selected low-risk patients or in cases that have comorbid limitations. The evidence also supports the importance of multidisciplinary care models where rheumatologists, pulmonologists, and cardiologists would collectively undertake treatment plans, adverse event monitoring and coordinating diagnostic-related follow-ups.

Within research perspectives there are still a number of gaps. On one hand, CTD-PAH is a poorly represented condition in randomized clinical trials and requires individualized trial design, where the heterogeneous nature and complexity of patients are reflected. Second, more definite data are required with regards to long-term outcomes, i.e. survival after three years, quality-of-life evidence and hospitalization rates. Last, prospective studies are needed to determine the effects of PAH-specific therapies on extracardiac involvement of the connective tissue disease, such as renal, musculoskeletal, and skin disease.

In summary, this review shows that there has been substantial progress regarding the treatment of CTD-PAH, but research and development are still the burning issues. Through the implementation of pharmacologic innovation and precision medicine and through community working together, more clinicians can achieve significant impact on the fate of patients with this life-threatening and rare cardiopulmonary complication.

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Conflicts of interest

The authors have no conflicts of interest to declare

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