J Bras Pneumol. 2020;46(2):e20190423
https://dx.doi.org/10.36416/1806-3756/e20190423

SPECIAL ARTICLE

Brazilian guidelines for the pharmacological treatment of idiopathic pulmonary fibrosis. Official document of the Brazilian Thoracic Association based on the GRADE methodology

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Submitted: 20 December 2019.
Accepted: 12 January 2020.

Study carried out by the Sociedade Brasileira de Pneumologia e Tisiologia, Brasília (DF) Brasil.

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a form of chronic interstitial lung disease of unknown cause, which predominantly affects elderly men who are current or former smokers. Even though it is an uncommon disease, it is of great importance because of its severity and poor prognosis. In recent decades, several pharmacological treatment modalities have been investigated for the treatment of this disease, and the classic concepts have therefore been revised. The purpose of these guidelines was to define evidence-based recommendations regarding the use of pharmacological agents in the treatment of IPF in Brazil. We sought to provide guidance on the practical issues faced by clinicians in their daily lives. Patients of interest, Intervention to be studied, Comparison of intervention and Outcome of interest (PICO)-style questions were formulated to address aspects related to the use of corticosteroids, N-acetylcysteine, gastroesophageal reflux medications, endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, pirfenidone, and nintedanib. To formulate the PICO questions, a group of Brazilian specialists working in the area was assembled and an extensive review of the literature on the subject was carried out. Previously published systematic reviews with meta-analyses were analyzed for the strength of the compiled evidence, and, on that basis, recommendations were developed by employing the Grading of Recommendations Assessment, Development and Evaluation approach. The authors believe that the present document represents an important advance to be incorporated in the approach to patients with IPF, aiming mainly to improve its management, and can become an auxiliary tool for defining public policies related to IPF.

Keywords: Idiopathic pulmonary fibrosis; GRADE approach; Pulmonary fibrosis/drug therapy; Practice guideline.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a form of chronic interstitial lung disease of unknown cause, limited to the lungs, which predominantly affects elderly men who are current or former smokers.[1-5] From a histological standpoint, IPF is characterized by the usual interstitial pneumonia pattern that can currently be inferred with a reasonable degree of certainty in cases of typical radiological findings on HRCT.[1-5] Even though it is an uncommon disease, IPF is of great clinical importance because of its severity. Although the natural history of the disease may vary and it is difficult to make accurate prognostic predictions for a given patient, the median survival for untreated patients with IPF is only 2.9 years.[6]

In recent decades, several pharmacological treatment modalities, with varied mechanisms of action, have been investigated for the treatment of IPF, and a substantial number of studies have reported negative outcomes.[7-36] Nevertheless, new drugs have shown benefits for the

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Financial support: None.

treatment of this disease, and some of them are already commercially available for this indication.

The purpose of these guidelines was to define evidence-based recommendations regarding the use of pharmacological agents in the treatment of IPF. We sought to provide guidance on the practical issues faced by clinicians in their daily routine. To that end, we carried out an extensive review of the literature on the subject, employing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[37] It should be noted that, to date, there have been no studies using a methodology similar to that employed here to address the topic in Brazil.

METHODOLOGY

The development of the guidelines began with the formation of a group of coordinators, which included two recognized specialists in the subject area and two specialists in methodology. Pulmonologists familiar with the care of patients with IPF, working in different regions of Brazil, were invited to join a specialist committee. Everyone involved in the process provided signed conflict-of-interest forms (Chart S1, supplementary material: http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=73).

In a face-to-face meeting, held in September of 2017 in the city of São Paulo, Brazil, the objectives of the project were defined. It was decided that the GRADE approach would be used and that priority would be given to questions related only to the pharmacological treatment of IPF. The specialists then received written materials and training videos related to each step of the GRADE approach.[38-40]

The specialists formulated Patients of interest, Intervention to be studied, Comparison of intervention and Outcome of interest (PICO)-style questions related to the pharmacological treatment of patients with IPF. Through an online voting process, seven PICO questions and their corresponding highest-scored outcomes were selected on the basis of degree of importance. The outcomes were classified as unimportant, important, or critical, taking into account the IPF patient perspective, in accordance with the GRADE approach (Chart 1).

A librarian searched for articles published in English in PubMed and EMBASE, following a standardized methodology, under the supervision of the methodologists (Chart S2). In our search strategy, we focused on systematic reviews with meta-analyses, using pre-established keywords and covering a period of 10 years or less, with an inclusion data limit of November 2018. A decision was made to employ a pragmatic strategy of searching for completed meta-analyses, rather than searching for clinical trials and subsequently performing meta-analyses.

After the preliminary selection of articles, the methodologists separately evaluated the articles by reviewing their titles and abstracts to decide which ones would be included in the guidelines. Disagreements were resolved by consensus. The next step involved qualitative analysis of the full texts of the selected articles, which was carried out by the two methodologists, working independently. Again, disagreements about inclusion or exclusion of articles were resolved by consensus. The selected articles were then evaluated by the specialist coordinators, each working separately, and agreement among the analyses regarding the inclusion or exclusion of articles was assessed. The reasons for excluding articles, as presented in Figures S1 through S7 of the supplementary material, were documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[41]

Tables summarizing the evidence for each question (Tables S1 through S7) were prepared following the GRADE approach, using the GRADEpro Guideline

Chart 1. Questions and corresponding outcomes selected for the development of these guidelines.

Question	Critical outcome	Important outcome	Unimportant outcome
1. Should we recommend the use of nintedanib for patients with IPF?	Mortality Decline in FVC Number of exacerbations	Quality of life	Adverse events
2. Should we recommend the use of pirfenidone for patients with IPF?	Mortality Decline in FVC Number of exacerbations	Quality of life	Adverse events
3. Should we recommend the use of phosphodiesterase-5 inhibitors for patients with IPF?	Mortality	Quality life Dyspnea	–
4. Should we recommend the use of endothelin-receptor antagonists for patients with IPF?	Mortality Decline in FVC	–	Adverse events
5. Should we recommend pharmacological treatment of gastroesophageal reflux for patients with IPF?	Mortality Decline in FVC Number of exacerbations Number of hospitalizations	–	–
6. Should we recommend the use of N-acetylcysteine for patients with IPF?	Mortality Decline in FVC	–	–
7. Should we recommend the use of corticosteroids for patients with IPF?	Mortality Decline in FVC	–	–

IPF: idiopathic pulmonary fibrosis.

Development Tool (GDT; McMaster University, HamiltonON, Canada).[42] The quality of the evidence for each meta-analysis included, as a function of each analyzed outcome, was classified as high, moderate, low, or very low (Chart 2).

The quality of evidence was reduced by one or two grades if a risk of bias, indirect evidence, inconsistency, imprecision, or publication bias was identified. In contrast, the quality of evidence was upgraded if there was a strong association, no plausible confounders, or a dose response relationship, or if all plausible confounders would have reduced the effect (Chart 3). In the GRADE approach, the quality of the studies determines the confidence level and degree of certainty of the estimated effect of the intervention on each of the outcomes selected.[40]

In September of 2019, the Coordinating Committee met face to face with the specialists, in the city of São Paulo, to review the results and all tables summarizing the evidence. The attending members reviewed the tables, and corrections were made as appropriate.

Recommendations based on critical outcomes were made for each question, following the GRADE approach (Chart 4). When there was no consensus, votes were taken, the results of which were documented (Chart S3). The recommendations could be either strong or conditional.[40] The term "we recommend" was used for strong recommendations, and the term "we suggest" was used for conditional recommendations. Factors influencing the strength of recommendation included the balance between benefits and undesirable consequences, the overall quality of evidence, patient values/preferences, costs, and resource allocation.

For the preparation of the manuscript, the text was divided among the participants, each of whom returned their sections to the specialist coordinators within certain deadlines. A preliminary version of the guidelines was then edited and sent to all of the participants for corrections and suggestions, in an interactive process. All of the individuals listed as authors take responsibility for the final text, in its entirety. The seven PICO questions, as well as the evidence, recommendations, and comments related to them, are described below.

QUESTION 1: SHOULD WE RECOMMEND THE USE OF NINTEDANIB FOR PATIENTS WITH IPF?

Nintedanib was initially developed as an inhibitor of VEGF and FGF receptors, being intended for use in the treatment of cancer.[43] However, since nintedanib inhibits PDGF receptors, it has also been investigated as a therapy for IPF.[43] Nintedanib competitively inhibits tyrosine kinases, which explains its many potential actions, such as impeding the migration and proliferation of myofibroblasts and fibroblasts, as well as the deposition of extracellular matrix. In addition, more recent evidence indicates that nintedanib can reduce TGF-β production, inhibit the formation of the collagen fibrin network, and stimulate surfactant protein D production.[44-46]

Chart 2. Quality of evidence interpretation following the Grading of Recommendations Assessment, Development and Evaluation system.[a]

Quality of evidence	Implication	Example
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect; we are confident that we can expect a very similar effect in the population for which the recommendation is intended	Randomized trials without serious limitations Well-performed observational studies with very large effects
Moderate ⊕⊕⊕◯	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	Randomized trials with serious limitations Well-performed observational studies yielding large effects
Low ⊕⊕◯◯	Further research is very likely to have a major impact on our confidence in the estimate of effect and is likely to change the estimate	Randomized trials with very serious limitations Observational studies without special strengths or important limitations
Very low ⊕◯◯◯	Any estimate of effect is very uncertain	Randomized trials with very serious limitations and inconsistent results Observational studies with serious limitations Unsystematic clinical observations (e.g., case series or case reports)

[a]Adapted from the Brazilian National Ministry of Health.[37]

Chart 3. Factors that can affect the quality of evidence.[a]

Quality of evidence	Reasons for downgrading	Reasons for upgrading
• High • Moderate • Low • Very low	• Risk of bias • Indirect evidence • Inconsistency • Imprecision • Publication bias	• A strong association, with no plausible confounders • Evidence of dose response • All plausible confounders would have reduced the effect

[a]Adapted from Guyatt et al.[38]

One phase II clinical trial and two phase III clinical trials, all observing subjects over a one-year period, evaluated the effects that nintedanib at a target dose of 150 mg twice daily had on the rate of decline in FVC.[27,28] On the basis of the results observed for this primary outcome, the US Food and Drug Administration approved nintedanib for use in patients with IPF.[47] The most common adverse effects of nintedanib, when it is used at the doses recommended for the treatment of IPF, are related to the gastrointestinal tract, especially diarrhea, of varying intensity, which, in the original clinical trials, affected approximately 62% of the participants who used the drug.[28]

Evidence

Using the methodology described above, we selected six systematic reviews with meta-analyses (Figure S1). [48-55] Even though not all of them analyzed the exact same sets of outcomes, they all indicate a beneficial therapeutic effect of nintedanib versus placebo in patients with IPF (Table S1).

With regard to mortality (a critical outcome), there was no statistically significant effect (OR = 0.70; 95% CI: 0.45-1.09) and the quality of evidence was moderate.[48]

With regard to a decline in FVC (a critical outcome), nintedanib was found to be beneficial. For a > 10% decline in FVC, the estimated OR was 0.61 (95% CI: 0.48-0.78), indicating a high quality of evidence.[48]

Finally, with regard to number of exacerbations (a critical outcome), nintedanib was found to be effective in reducing the number of acute exacerbations (OR = 0.50; 95% CI: 0.31-0.79), indicating a moderate quality of evidence.[54]

Recommendation

For patients with IPF, we suggest using nintedanib (conditional recommendation; moderate quality of evidence).

Comments

The available meta-analyses included only randomized, double-blind, controlled clinical trials. Therefore, the results obtained apply primarily to patients who meet the same selection criteria as those used for the participants in those trials. Those trials did not include patients with very early-stage IPF (DLCO ≥ 80%) or very advanced IPF (FVC < 50% of predicted or DLCO < 30%).

Therefore, the effects of nintedanib in these two groups of patients have yet to be well characterized. In addition, it is not possible to determine, on the basis of the selected articles, the long-term efficacy and safety of nintedanib, because the maximum duration of the trials included here was 52 weeks.

The recommendation made implies that using nintedanib is the right course of action to be taken in 50-95% of cases.[42] Clinicians should acknowledge that different choices may be appropriate for individual patients and that they are responsible for helping patients and families make decisions consistent with their values and preferences (Chart 4).[37-42] This recommendation does not take into account cost analyses or aspects of drug economics.

QUESTION 2: SHOULD WE RECOMMEND THE USE OF PIRFENIDONE FOR PATIENTS WITH IPF?

Pirfenidone is a drug with anti-inflammatory and antifibrotic properties that acts through regulation of TNF-α and TGF-β pathways, as well as through modulation of cellular oxidation.[56] Ultimately, pirfenidone inhibits fibroblast proliferation, consequently decreasing collagen synthesis and deposition.[56-59]

The therapeutic potential of pirfenidone was initially demonstrated in two small clinical trials, which compared it with placebo.[16,20] Subsequently, three other clinical trials stood out for greater homogeneity of inclusion

Chart 4. Implications of the recommendations of the Grading of Recommendations Assessment, Development and Evaluation system.[a]

Target audience	Strong recommendation		Conditional recommendation	
	We recommend	We do not recommend	We suggest	We do not suggest
Patients	Most individuals would want the intervention to be recommended, and only a small number would not accept this recommendation	Most individuals would not want the intervention to be recommended, and only a small number would accept this recommendation	Most individuals would want the intervention to be recommended, although a considerable number would not accept this recommendation	Most individuals would not want the intervention to be recommended, although a considerable number would accept this recommendation
Health professionals	Most patients should receive the recommended intervention		The health professional should acknowledge that different choices may be appropriate for individual patients and should help them make a decision consistent with their values and preferences	
Administrators	The recommendation can be adopted as a health policy in most situations		Substantial debate and involvement of all stakeholders are required	

[a]Adapted from Guyatt et al.[39] and Andrews et al.[40]

criteria and outcomes, including assessment of > 10% decline in FVC at week 52.[25,26] Those three clinical trials, in a combined analysis, demonstrated a reduced decline in percentage predicted FVC, as well as a reduced risk of disease progression, with the use of a target dose of 2,403 mg/day. In the five clinical trials, adverse events were more common in the group receiving pirfenidone, being mainly related to the skin (rash and photosensitivity) and the gastrointestinal tract (nausea, dyspepsia, and loss of appetite).

Evidence

Nine systematic reviews with meta-analyses comparing pirfenidone with placebo were selected (Figure S2).[55,60-65] The meta-analyses evaluated several outcomes, including mortality, progression-free survival, acute exacerbation, functional decline, change in six-minute walk distance (6MWD), and adverse events, indicating that pirfenidone has a favorable therapeutic effect and an acceptable safety profile.

Table S2 summarizes the quality of evidence of the selected articles for the question related to pirfenidone. Pirfenidone treatment was shown to reduce mortality—relative risk (RR) = 0.53; 95% CI: 0.32-0.88, indicating a moderate quality of evidence. [61,62] Likewise, pirfenidone was found to be effective in reducing the occurrence of a > 10% decline in FVC (RR = 0.64; 95% CI: 0.50-0.83).[61,62] With regard to the reduction in the number of acute exacerbations, there was no statistically significant effect (RR = 0.59; 95% CI: 0.19-1.84), indicating a low quality of evidence.[61,62]

Recommendation

For patients with IPF, we suggest using pirfenidone (conditional recommendation; low quality of evidence).

Comments

The available systematic reviews and meta-analyses evaluating the use of pirfenidone in patients with IPF included only randomized, double-blind, controlled clinical trials. The results obtained apply to patients who meet the same selection criteria as those used for the participants in those trials, that is, patients with mild to moderate disease. Those trials did not include IPF patients who had very early-stage functional changes (DLCO ≥ 90%), had very advanced functional changes (FVC < 50% of predicted or DLCO < 30%), or were over 80 years of age. Therefore, the effects of pirfenidone in those subgroups of patients have yet to be determined. On the basis of the results found, it is not possible to determine the impact of pirfenidone in terms of long-term efficacy and safety, because the maximum duration of the trials included here was 72 weeks.

The recommendation made implies that using pirfenidone is the right course of action in 50-95% of cases.[42] Clinicians should acknowledge that choices need to be individualized and that they should help patients and their families make decisions consistent with their values and preferences (Chart 4).[37-42] This recommendation does not take into account cost analyses or aspects of drug economics.

QUESTION 3: SHOULD WE RECOMMEND THE USE OF PHOSPHODIESTERASE-5 INHIBITORS FOR PATIENTS WITH IPF?

Phosphodiesterase-5 (PDE5) inhibitors stabilize cyclic guanosine monophosphate, the second messenger of nitric oxide, leading to pulmonary vasodilation.[66] The vasodilation produced by PDE5 inhibitors appears to have a preference for well-ventilated lung tissue, which could improve the ventilation-perfusion ratio and gas exchange in patients with IPF.[66] In addition, pulmonary hypertension is a common finding in patients with IPF, being associated with higher rates of morbidity and mortality.[67] The commercially available PDE5 inhibitors are sildenafil, tadalafil, and vardenafil; however, only sildenafil has been tested in patients with IPF.

Three clinical trials, of which only two were randomized, have evaluated the effects of sildenafil in patients with advanced IPF.[68-70] The primary outcome used was always a change in the 6MWD, which was not achieved in any of the investigations. Sildenafil treatment also had no impact on exacerbation or mortality rates.

Evidence

As a result of the methodology employed for these guidelines, two systematic reviews with meta-analyses were selected (Figure S3 and Table S3). One of those reviews found no evidence that sildenafil can provide relief of dyspnea in patients with IPF (relative risk not estimable; very low level of evidence) or improve quality of life in patients with IPF (relative risk not estimable; very low level of evidence).[71] The other meta-analysis, which used a network methodology, evaluated the effects of sildenafil treatment on mortality in patients with IPF, thus finding that the death rates in the treatment group and placebo group were 2.9% and 8.5%, respectively.[55] However, the OR was 0.84 and did not reach statistical significance (95% CI: 0.31-2.41).

Recommendation

For patients with IPF, we suggest not using a PDE5 inhibitor (conditional recommendation; moderate quality of evidence).

Comments

The critical outcome selected for this question by the specialists working on these guidelines was mortality. With regard to this parameter, the selected articles did not show significant benefits of PDE5 inhibitors. The same was true for two outcomes classified as important: dyspnea and quality of life. It is of note that other guidelines for the treatment of IPF, developed by other medical societies, also do not recommend the use of a PDE5 inhibitor (sildenafil) for this group of patients.[4,72,73] In addition, a randomized clinical trial

comparing the use of nintedanib plus sildenafil with that of nintedanib alone in patients with IPF and a DLCO < 35% of the predicted value, which was published after the analysis of the articles selected for these guidelines had been completed, found no significant differences regarding quality of life or dyspnea.[34] A pre-specified analysis of the subgroup of patients with right ventricular dysfunction, published separately, also showed no impact on the relevant variables.[74]

QUESTION 4: SHOULD WE RECOMMEND THE USE OF ENDOTHELIN-RECEPTOR ANTAGONISTS FOR PATIENTS WITH IPF?

Although the pathogenesis of IPF has yet to be fully elucidated, endothelin-1, a potent vasoconstrictor and growth factor, has been related to the fibroproliferative process of IPF.[75] Endothelins have a potent proliferative effect on mesenchymal cells and can induce cell differentiation, increasing the synthesis and deposition of extracellular matrix components, as well as their contractility.[75] On the basis of these elements, clinical trials of endothelin-receptor antagonists have been conducted with the aim of reducing the fibrotic process.

Two clinical trials have evaluated the efficacy of bosentan versus that of placebo in patients with IPF. No significant effects of bosentan were detected, either on the primary outcome (6MWD) or on the rate of disease progression, quality of life, or dyspnea intensity.[18,22,76]

The effect of macitentan on the rate of decline in FVC in patients with IPF was also not significant in comparison with that of a placebo.[24] Finally, one study investigating the effects of ambrisentan versus those of placebo in patients with IPF was terminated early because an interim analysis showed that ambrisentan-treated patients were more likely to meet the criteria for disease progression and had a greater number of respiratory hospitalizations.[23]

Evidence

Using the methodology proposed above, we selected two review articles with meta-analyses (Figure S4). Both evaluated individual results for bosentan, macitentan, and ambrisentan.[48,55] None of the drugs investigated showed significant effects with regard to mortality (critical outcome) or adverse effects (unimportant outcome; Table S4).

Recommendation

For patients with IPF, we recommend not using endothelin-receptor antagonists (strong recommendation; low quality of evidence).

Comments

In addition to the fact that the available evidence indicates no significant effects of endothelin-receptor antagonists on relevant clinical outcomes, it has been suggested that the use of ambrisentan, in particular, is associated with deleterious effects. It is unlikely that further studies of this class of drugs in patients with IPF will be conducted.

QUESTION 5: SHOULD WE RECOMMEND PHARMACOLOGICAL TREATMENT OF GASTROESOPHAGEAL REFLUX FOR PATIENTS WITH IPF?

Gastroesophageal reflux (GER) is highly prevalent in patients with IPF and, although there is as yet no evidence of a causal relationship, chronic aspiration is considered a risk factor for disease progression and exacerbation.[77-79] Although the importance of microaspiration of gastric content in the pathogenesis of IPF has yet to be established, there have been anecdotal reports of stabilization and (clinical and functional) improvement in patients with IPF after pharmacological or surgical treatment of GER.[80,81] Recent international guidelines suggest regular antacid use for all patients with IPF, although the quality of evidence is very low.[3,4]

All of the studies evaluating the possible effects of pharmacological treatment of GER in patients with IPF have been observational, and most have used data derived from the placebo arms of clinical trials aimed at investigating other drugs.[82-86] To date, there have been no clinical trials with an appropriate design and an adequate number of volunteers that have evaluated the routine use of GER medications in symptomatic or asymptomatic patients with IPF.[87]

Evidence

The methodology employed in developing these guidelines did not allow us to select articles suitable for developing recommendations regarding pharmacological treatment of GER in patients with IPF (Figure S5 and Table S5).

Recommendation

For patients with IPF, there is insufficient evidence to make a recommendation for or against the use of pharmacological treatment of GER.

Comments

Studies evaluating the possible effects of pharmacological treatment of GER in patients with IPF have involved patients who had been randomized to the placebo arms of clinical trials of other drugs for IPF. [82-86] This strategy introduces a very large selection bias, because it is not possible to know why pharmacological treatment of GER was prescribed, and these patients may therefore not be representative of all patients with IPF. Further controlled randomized clinical trials of pharmacological treatment of GER are needed in order to properly elucidate its effects in patients with IPF. Given that pharmacological treatment of GER may be associated with potential adverse effects, its use should be evaluated on a case-by-case basis and should be considered in patients with symptoms suggestive of GER or with GER symptoms confirmed by ancillary tests.

QUESTION 6: SHOULD WE RECOMMEND THE USE OF N-ACETYLCYSTEINE FOR PATIENTS WITH IPF?

N-acetylcysteine (NAC) is a precursor drug to glutathione, a water-soluble antioxidant present in most cells in the body.[88] A potential contribution of oxidative stress to the progression of IPF has led to studies being conducted to determine whether the use of NAC could restore lung glutathione levels.[88,89] Thus, NAC could slow the progression of the disease.

A multicenter double-blind, placebo-controlled study evaluated the use of oral NAC plus a corticosteroid and azathioprine versus placebo.[11] Participants who received NAC plus a corticosteroid and azathioprine had a significant reduction in the rate of decline in FVC and in DLCO.[11] In contrast, studies of inhaled or oral NAC monotherapy versus placebo demonstrated no significant differences in the evolution of lung function or in other clinical outcomes.[90-92]

Evidence

We selected five systematic reviews with meta-analyses comparing NAC and placebo with regard to mortality, as well as one evaluating reductions in the rate of decline in FVC in the treatment of IPF (Figure S6 and Table S6).[48,55]

In comparison with placebo, NAC did not reduce mortality in patients with IPF (OR = 0.84; 95% CI: 0.20-4.50).[54] With regard to the reduction in the rate of decline in FVC at 12 months, it was not possible to estimate the effect of NAC versus that of placebo because of the heterogeneity of and high risk of bias within the studies selected for the meta-analysis.[48]

Recommendation

For patients with IPF, we suggest not using NAC (conditional recommendation; low quality of evidence).

Comments

The lack of effect of NAC on reducing mortality and the difficulty in estimating positive effects of NAC on reducing the rate of decline in FVC make it unlikely that the drug has any beneficial effects on the course of IPF. It has been suggested that IPF patient responses to the use of NAC may be influenced by *TOLLIP* gene polymorphisms.[93] However, these aspects still require further clarification so that robust conclusions can be drawn.

QUESTION 7: SHOULD WE RECOMMEND THE USE OF CORTICOSTEROIDS FOR PATIENTS WITH IPF?

Classical hypotheses regarding the pathogenesis of IPF suggest that the onset of the disease is due to an inflammatory process, in which proinflammatory cytokines released by alveolar macrophages play a decisive role.[94,95] In this context, the use of corticosteroids would potentially be beneficial to the clinical course of patients with IPF. However, the most widely accepted hypothesis for the pathogenesis of IPF is alveolar epithelial aggression and damage followed by release of profibrotic mediators, with abnormal repair, myofibroblastic proliferation, and collagen deposition, without evident inflammation.[96]

The current concept of IPF was formulated in 2000; since then, there have been no controlled clinical trials of corticosteroid monotherapy in patients with IPF.[1]

Evidence

Within the literature review date range pre-established for these guidelines, it was not possible to find any systematic reviews or meta-analyses evaluating the effects of corticosteroid monotherapy versus those of placebo in the treatment of IPF (Figure S7 and Table S7).

Recommendations

For patients with IPF, there is insufficient evidence to make a recommendation for or against the use of corticosteroids.

Comments

Although there is no evidence regarding the use of corticosteroids in IPF, it is unlikely that studies of these drugs in patients with IPF will be conducted, because, given the noninflammatory pathogenesis of the disease, there appears to be little chance of therapeutic success. This recommendation is intended for patients with stable IPF. The potential use of corticosteroids in patients with acute IPF exacerbations was not analyzed in these guidelines.

FINAL CONSIDERATIONS

A summary of the recommendations for the pharmacological treatment of IPF is shown in Chart 5.

Although there is currently no drug that can cure IPF, these guidelines suggest that nintedanib and pirfenidone be considered for the treatment of the disease (conditional recommendation). The evidence indicates that these antifibrotic agents are, in fact, the only pharmacological treatment options that can lead to a reduction in functional decline in IPF. Both reduce the rate of decline in FVC, which is a strong independent predictor of IPF mortality. However, when considering whether or not to use either of these drugs, it is essential to evaluate the specifics of each case, including the severity of the functional impairment, the presence of comorbidities, the concomitant use of other drugs (i.e., potential drug interactions), potential adverse events, and costs, as well as, in particular, the concerns of patients and their families. It should also be emphasized that nintedanib and pirfenidone were not compared with each other in our guidelines, and determining the superiority of one over the other is therefore not possible. In addition, the combined use of these drugs was not evaluated.

Although the prevalence of GER is high in IPF, we found insufficient evidence to define the role of the routine use of GER medications in patients with IPF.

Chart 5. Summary of the recommendations for the pharmacological treatment of idiopathic pulmonary fibrosis.

Question	Recommendation	Grade of recommendation	Quality of evidence
1. Should we recommend the use of nintedanib for patients with IPF?	Yes (suggestion)	Conditional	Moderate
2. Should we recommend the use of pirfenidone for patients with IPF?	Yes (suggestion)	Conditional	Low
3. Should we recommend the use of phosphodiesterase-5 inhibitors for patients with IPF?	No (suggestion)	Conditional	Moderate
4. Should we recommend the use of endothelin-receptor antagonists for patients with IPF?	No (recommendation)	Strong	Low
5. Should we recommend pharmacological treatment of gastroesophageal reflux for patients with IPF?	Unknown Lack of eligible studies for selection		
6. Should we recommend the use of N-acetylcysteine for patients with IPF?	No (suggestion)	Conditional	Low
7. Should we recommend the use of corticosteroids for patients with IPF?	Unknown Lack of eligible studies for selection		

IPF: idiopathic pulmonary fibrosis.

Again, the decision should be made on the basis of the clinical characteristics of each case.

The lack of reliable data does not allow recommendations to be made regarding the use of corticosteroids in IPF. That does not imply that this category of drugs might not be used in other forms of interstitial lung disease, such as sarcoidosis and proliferative bronchiolitis.

With regard to the other drugs investigated, it is suggested that neither a PDE5 inhibitor nor NAC be used (conditional recommendation), and it is strongly recommended that endothelin-receptor antagonists not be prescribed for patients with IPF.

It should be emphasized that non-pharmacological approaches to IPF, including oxygen supplementation, pulmonary rehabilitation, immunizations, and lung transplantation, were not considered in the development of these guidelines. It should also be emphasized that the guidelines in question apply only to patients with IPF, which means that the results cannot be extrapolated to patients with fibrotic lung diseases from other causes.

We believe that the present document represents an important tool to be incorporated in the approach to patients with IPF, aiming mainly to improve its management, as well as aiding in the development of public policies related to the disease.

ACKNOWLEDGMENTS

We would like to thank Luana Campos for conducting the search for articles in the selected databases. We would also like to thank the Brazilian Thoracic Association Board of Directors for their support for the development of these guidelines.

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