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RESEARCH ARTICLE

A STUDY ON PIRFENIDONE VERSUS NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN A TERTIARY CARE HOSPITAL: A CROSS SECTIONAL STUDY

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic condition with a poor prognosis and have an average life expectancy of 3-4 years. Two antifibrotic treatments have been approved to treat IPF: nintedanib and pirfenidone. These medications lower the decline in lung function and lower the risk of acute respiratory deterioration, which is linked with a high morbidity and death.Individual clinical trials have not been powered to demonstrate mortality decreases, however analysis of pooled data from clinical trials and observational research imply that anti-fibrotic drugs increase life expectancy. This study describes the utility of anti-fibrotic drugs and compare their efficacy.

Methods and Materials: This 6 month cross-sectional study conducted at Santhiram Medical College and General Hospital in Nandyal.In patients with IPF , Clinical, functional and radiological data were gathered at baseline and during the follow-up, as per our Center procedure.This study compares and evaluates the efficacy of nintedanib and pirfenidone. A total of 40 patients over the age of 18 with IPF diagnosis were included. Patients under 18 years , those with known fibrosing lung diseases, bronchial asthma, COPD, HIV, Tuberculosis, or other organ failures were excluded.

Results: At baseline, IPF patients treated with Pirfenidone had Forced vital capacity(FVC) and Forced expiratory volume at 1 second(FEV1) predicted percentages of 63.57 ± 8.34% and 72.31 ± 4.91%, respectively. In IPF patients treated with Nintedanib, at baseline(time 0), FVC and FEV1 percentages were 60.15±8.82% and 72.31±4.91% respectively. There were no significant variations in FVC and FEV1 percentages at time 0 between patients treated with the two medications (p=0.23,p=0.7,respectively).

At 3-month follow-up, patients treated with Pirfenidone had predicted FVC and FEV1 values of 65.73 ± 7.84% and 72.94 ± 4.45%, respectively, whereas patients treated with Nintedanib had predicted valuesof 65.75 ± 7.67% and 72.42 ± 4.45%.

At 6-month follow-up, patients on Pirfenidone had predicted FVC and FEV1 values of 66.9 ± 8.72% and 73.5 ± 4.50%, respectively. Nintedanib treatment resulted in 67.7±8.46% and 72.94±4.51% outcomes.

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Conclusion: our study shown that pirfenidone and nintedanib are equally effective at reducing FVC decline over a 6-month time frame.While nintedanib was slightly more beneficial in lowering FVC decline during the 6-month period. Both drugs were well tolerated, while nintedanib showing good tolerance in the majority of IPF patients.

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Introduction:-

Idiopathic pulmonary fibrosis is a chronic, progressive Interstitial lung disease (ILD) that affects the lungs. The cause of the disease is unknown[1, 2]. About 25% of all Interstitial lung disorders (ILD) and roughly 55% of all Idiopathic interstitial pneumonias (IIP) are caused by IPF[3]. It is more common in between the ages of 65 and 79. Its annual incidence is 0.22–7.4 instances per 100,000 people, and its prevalence is 1.25–23.4 cases per 100,000 people[3].It is a deadly illness with a bad prognosis that is debilitating[1, 2, 3, 4, 5, 6] .20–40% of people survive after five years.Stabilize or lower the rate of illness progression is the aim of IPF treatment[7].Pathogenesis is characterized by aberrant overexpression of profibrotic pathways, triggered by oxidative-nitrosative stress and alveolar epithelial injury refractory to anti-inflammatory and immunosuppressant treatments[8,9,10,11].

Real-life studies have confirmed the effectiveness of pirfenidone and nintedanib in slowing the progression of IPF, suggesting an improvement in survival rate (Fisher et al., 2017; Margaritopoulos et al., 2018; Lancaster et al., 2019) but without any substantial effect on quality of life[.12,13,14,15]

IPF diagnosis is made when a typical usual interstitial pneumonia (UIP) histopathologic pattern or in high-resolution computed tomography (HRCT) chest without a known cause. Breathlessness ,cough and respiratory insufficiency are the main symptoms of IPF, which also typically results in mortality. Drug development for IPF has concentrated on compounds that are believed to target fundamental fibrosis processes. In large randomized placebo-controlled trials, nintedanib and pirfenidone showed a slowing in the decline of lung function while maintaining an acceptable safety and tolerability profile. This led the US Food and Drug Administration to approve both drugs in 2014.

Nintedanib is an intra cellular inhibitor of tyrosine kinases, including the fibro blast growth factor receptor, platelet-derived growth factor receptor, and vascular endothelial growth factor (VEGF) receptor, as well as the non receptor members of the Src family. It has shown anti-fibrotic and anti-inflammatory effects by interfering with fibroblast proliferation, migration, and differentiation as well as the release of extracellular matrix components in the lung[16,17]

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally bio-available synthetic molecule. It was shown to regulate the activity of transforming growth factor (TGF) β and tumour necrosis factor (TNF) α.[18,19]

Both Nintedanib and Pirfenidone reduced FVC decline consistently across subgroups defined based on a variety of baseline characteristics[20]

Materials and Methods:-

This six-month (january2024 -July 2024) study was conducted on patients with idiopathic pulmonary fibrosis at Santhiram Medical College and General Hospital in Nandyal. Before initiating therapy, each patient provided informed consent, which was approved by our Ethics Committee. This study evaluated and compared the efficacy of PirfenidoneandNintedanib.

IPF was diagnosed using the criteria established by the American Thoracic Society and the European Respiratory Society guidelines. Data were recorded. At baseline, we collected socio-demographic variables (age, gender, smoking status, employment history), clinical parameters (BMI, dyspnea, co-morbidities), HRCT chest, ANA profile, RA factor, dyspnea score and pulmonary function tests (PFTs).

A total of 40 patients of age >18 years with IPF diagnosed and who have given informed consent were included. Patients of age <18 years and other fibrosing lung diseases with known etiology ,Bronchial Asthma ,COPD, HIV, Tuberculosis, and patients with other organ failures and who have not given consent were excluded. 20 patients were

scheduled for pirfenidone treatment and 20 received nintedanib. Pirfenidone treatment was started by gradually increasing the dose over a 2-week period from 267 mg daily to 801 mg daily to 2403 mg daily divided into three doses. Nintedanib was started at a dose of 150 mg twice daily. Subsequently, patients were followed with regular visits at 3-month intervals with pulmonary function testing by spirometry, liver function monitoring, and recording of side effects and treatment compliance.All were enrolled in the follow-up program,. Their "chronic" therapy for any other comorbidity was left unchanged.The primary out come of this study was to assess the trend of lung function parameters like Forced vital capacity (FVC) and Forced expiratory volume at 1 sec during a 6-month period, as well as to document any adverse effects and the rate of reduction in disease development, which was defined as an improvement in FVC% of expected at 6 months.percent predicted FVC (FVC%), percent predicted FEV1 (FEV1%), were measured using spirometry,a lung function testing device .The differences between post- and pre-treatment lung function parameters were tested (i.e. pirfenidone vs nintedanib)

Statistical analysis

All data were recorded in a master chart using microsoft excel spread sheet analyzed by SPSS 25and data expressed as mean ± standard deviation . Statistical significance was set at $p < 0.05$.

Results:-

In present study Pirfenidone was administered to 20 individuals, and Nintedanib to another 20. The mean age of individuals treated with Pirfenidone was 66.94±8.682 years, while those treated with Nintedanib had a mean age of 68.21±10.047 years. Patients treated with Nintedanib had a considerably higher median age compared to those in the other group ($p<0.0001$). Males make nearly 75% of our IPF population, with no difference between groups (table 1). The smoking history indicated 60% of smokers in the Pirfenidone group and 70% in the Nintedanib group.Patients reported similar symptoms of exertional dyspnea and dry cough across all groups.

Table 1:- Clinical characteristics of IPF patients treated with pirfenidone and nintedanib.

Clinical parameters	Pirfenidone	Nintedanib
Mean age±S.D	66.94±8.682	68.21±10.047
sex	Males-14(70%) Females-6(30%)	Males-16(80%) Females-4(20%)
Dyspnea	75%	70%
Dry cough	70%	75%
Bi basilar crepts	100%	100%
Hrct chest-UIP pattern	100%	100%
Smokers	60%	70%

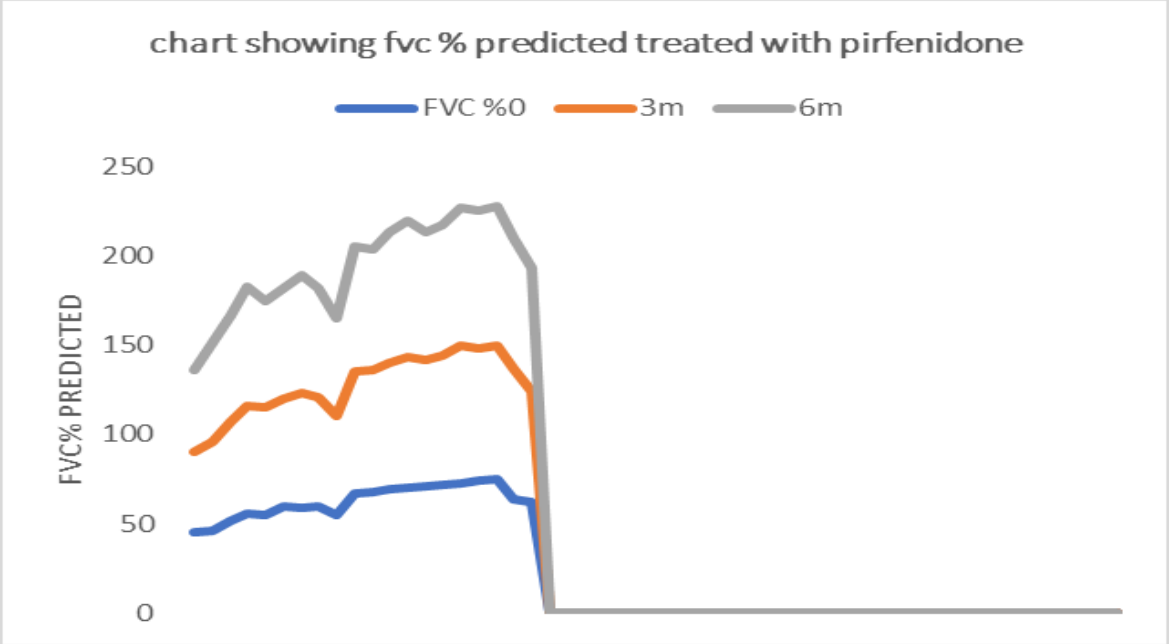
Table 2:- Showing comparison of spirometry parameters.

parameter	Mean ± SD	
	pirfenidone	nintedanib
FVC% predicted Baseline(0months)	63.57 ±8.34	60.15 ±8.82
At 3 months	65.73± 7.84	65.75± 7.67
At 6 months	66.9 8.±72	67.7 ±8.46
FEV1%predicted Baseline(0months)	72.31 ±4.91	71.26 ±4.91
At 3 months	72.94 ±4.45	72.42 ±4.45
At 6 months	73.5 ±4.50	73.94 ±4.51

Lung function test parameters at time base line in the population of IPF patients treated with Pirfenidone , FVC, FEV1 percentages were 63.57 ± 8.34% predicted values, 72.31 ± 4.91% predicted respectively. lung function test parameters at time 0 in the population of IPF patients treated with Nintedanib, At time 0, FVC, FEV1 percentages were 60.15± 8.82% predicted, 72.31 ± 4.91% predicted respectively. No significant differences in FVC, FEV1percentages were found at time 0 between patients treated with the two drugs ($p = 0.23$, $p = 0.7$ respectively).

At 3-month follow-up, patients treated with Pirfenidone had predicted FVC and FEV1 values of 65.73 ± 7.84% and 72.94 ± 4.45%, respectively, while patients treated with Nintedanib had predicted values of 65.75 ± 7.67% and 72.42 ± 4.45%, respectively(p=0.44,p=0.58).
At 6-month follow-up, patients treated with Pirfenidone had predicted FVC and FEV1 values of 66.9 ± 8.72% and 73.5 ± 4.50%, respectively.

Nintedanib treatment resulted in 67.7±8.46% and 73.94±4.51%(p=0.54,p=0.35) predicted outcomes.



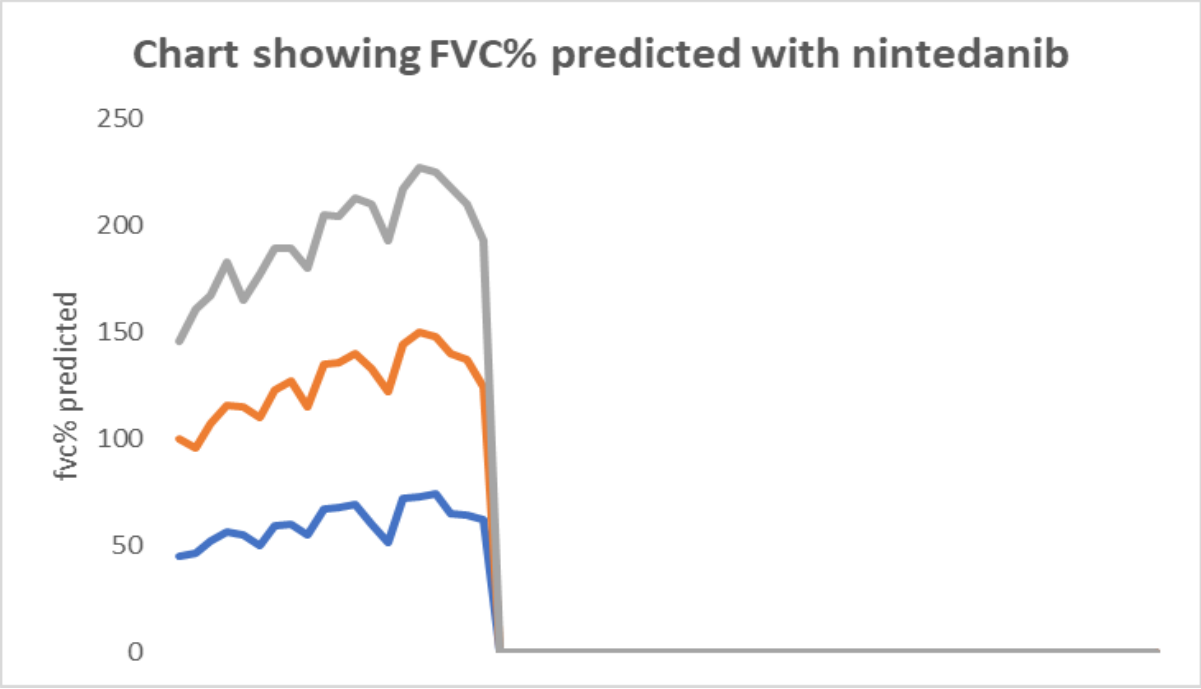


Table 3:- Showing adverse effects associated with two drugs.

Adverse effects	Pirfenidone	Nintedanib

Nausea/vomiting	3(15%)	2(10%)
dypepsia	2(10%)	1(5%)
diarrhea	1(5%)	3(15%)
fatigue	0	0
Photosensitivity rash	1(5%)	0
Elevated liver enzymes	1(5%)	1(5%)
anorexia	1(5%)	0
Weight loss	0	0

Both drugs show good tolerability profile in our study population. Despite the small frequency of side effects (particularly nausea,vomiting with pirfenidone and diarrhea with nintedanib), the majority were minor and easily treated with supportive therapy, short dose decreases. No fatalities were reported in our sample, demonstrating the two medications' good safety profile even in vulnerable patients over a 6 month observation period.

The gastrointestinal problems were the most common side effects of pirfenidone. The most common was dyspepsia and nausea, which occurred in 15% of cases. Dyspepsia and cutaneous rash followed in 5% of instances. Most patients' gastrointestinal adverse effects improved with the use of prokinetic medications and proton-pump inhibitors in addition to applying a broad-spectrum sunscreen.

Nintedanib therapy was well tolerated; the most common side effect, which affected 15% of patients, was diarrhoea, which resolved after the drug dosage was reduced from 150 to 100 mg twice a day. In addition, 5% of patients experienced elevated liver enzymes,elevated aminotransferase concentrations were generally corrected with dose modification, requiring no stop.

Discussion:-

Limited data is currently available about real-life experience with antifibrotic drugs in IPF patients[21,22,23]our population showed a clear predominance of males and most patients were smokers. The prevalence of males and smoking in our population, as well as the mean age of patients are in line with epidemiological studies[24,25]

Our study considered patients without distinction of age. In this study,The mean age of those treated with Pirfenidone was 66.94±8.682 years compared to 68.21±10.047 years of those treated with Nintedanib.In other studies,Bonella.F et al.,The mean age was 71 (SD ± 8) with a baseline FVC% predicted of 64 (±17).[26].mean age of onset: 71 ± 11 years, mean age at baseline were74 ± 9 years [27.]

Our results confirm the effectiveness of pirfenidone and nintedanib in slowing disease progression in terms of FVC reduction rate and in maintaining the effect in subsequent months of treatment[28].

A German study of 64 patients indicated that 67% of patients had stable FVC at 6 months following commencement of nintedanib.Diffusing capacity readings stabilizing after drug initiation validates anticipated therapeutic success and generally stable FVC levels during follow-up. Pitre et al. conducted a systematic review and network meta-analysis, which highlighted in lowering FVC decline (2.92%; 1.51 to 4.14)[29]

Our results on drug tolerance are consistent with prior studies (Lancaster et al., 2017; Rodríguez-Portal, 2018).[30,31]Despite the small frequency of side effects (particularly nausea,vomiting with pirfenidone and diarrhea with nintedanib), the majority were minor and easily treated with supportive therapy, short dose decreases. No fatalities were reported in our sample.However, the incidence of nausea in the CAPACITY 1 and 2 studies was as high as 36%.In this study, reducing the amount of pirfenidone resulted in reduced gastrointestinal symptoms. Even at a modest dose of 1200 mg/day, the medicine was effective in slowing the fall in FVC . Rather of discontinuing pirfenidone therapy, it should be explored to continue it with a reduced dose.This study had a lower incidence of photosensitivity than the Japanese clinical trials, which had a rate of 51%.The most common side effect with nintedanib was diarrohea, which occurred in 15% of patients and improved after reducing the dose from 150 to 100 mg twice a day. The open-label extension of the TOMORROW and INPULSIS studies indicates that nintedanib's beneficial effects last longer than a year[14,15] It has been shown that lowering the dose to 100mg twice daily does not significantly impact the efficacy of nintedanib[32].5% of individuals had abnormal liver enzymes, which were

reversible with dose decrease. Elevated aminotransferase concentrations were also reversible with dose adjustment and no withdrawal was needed.

In the TOMORROW study 55.3% of patients receiving nintedanib at 150 mg twice daily suffered diarrhoea. Other commonly reported AEs in the INPULSIS trials included nausea (24.5%), vomiting (11.6%) and weight loss (9.7%) A higher proportion of patients suffered a rise in alanine transaminase (ALT) or aspartate transaminase (AST) above the upper limit of normal (ULN) in the group taking nintedanib [33].A Greek CUP study involving 94 patients identified AEs with diarrhoea (55.3%) the most commonly reported event followed by weight loss (20.2%)[34].

Conclusion:-

In summary,This study compared the efficacy of two presently approved pharmacological therapies for IPF and found equal efficacy in lowering functional decline with acceptable tolerability while nintedanib was slightly more beneficial in lowering FVC decline during the 6-month period , even in participants with severe functional impairment. Both drugs were well tolerated, while nintedanib showed a good tolerability profile in the majority of IPF patients . Long-term multicenter prospective studies, including patient populations excluded from randomized clinical trials, are needed to validate our findings.Despite the small cohort size, it appears that ongoing treatment with either drug would be suggested to preserve lung function.

Limitations-

Our study has some limitations. First, it was not a randomized controlled trial.Second, the study population was relatively small and heterogeneous among groups.However, the number of patients enrolled was consistent with the majority of trials reported. The study's duration was short, and there was no control group.

Conflict of interest

The authors have no conflicts of interest to declare.

References:-

1. Cottin, V., Capron, F., Grenier, P., & Cordier, J. F. (2004). Diffuse idiopathic interstitial pneumonias. International multidisciplinary consensus classification by the American Thoracic Society and the European Respiratory Society, principal clinico-pathological entities, and diagnosis. Revue des maladies respiratoires, 21(2 Pt 1), 299-318.
2. Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., ... & Schunemann, H. J. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American journal of respiratory and critical care medicine, 183(6), 788-824.
3. Nalysnyk, L., Cid-Ruzafa, J., Rotella, P., & Esser, D. (2012). Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. European Respiratory Review, 21(126), 355-361.
4. Richeldi, L., Kreuter, M., Selman, M., Crestani, B., Kirsten, A. M., Wuyts, W. A., ... & Costabel, U. (2018). Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax, 73(6), 581-583.
5. King Jr, T. E., Bradford, W. Z., Castro-Bernardini, S., Fagan, E. A., Glaspole, I., Glassberg, M. K., ... & Noble, P. W. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New England journal of medicine, 370(22), 2083-2092.
6. Nathan, S. D. (2017). Evaluating new treatment options. Am J Manag Care, 23(11), S183-S190.
7. Taniguchi, H., Ebina, M., Kondoh, Y., Ogura, T., Azuma, A., Suga, M., ... & Pirfenidone Clinical Study Group in Japan. (2010). Pirfenidone in idiopathic pulmonary fibrosis. European Respiratory Journal, 35(4), 821-829.
8. Wolters, P. J., Collard, H. R., & Jones, K. D. (2014). Pathogenesis of idiopathic pulmonary fibrosis. Annual Review of Pathology: Mechanisms of Disease, 9(1), 157-179.
9. Sgalla, G., Iovene, B., Calvello, M., Ori, M., Varone, F., & Richeldi, L. (2018). Idiopathic pulmonary fibrosis: pathogenesis and management. Respiratory research, 19, 1-18.
10. Wuyts, W. A., Kolb, M., Stowasser, S., Stansen, W., Huggins, J. T., & Raghu, G. (2016). First data on efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of≤ 50% of predicted value. Lung, 194, 739-743.
11. Cameli, P., Carleo, A., Bergantini, L., Landi, C., Prasse, A., & Bargagli, E. (2020). Oxidant/antioxidant disequilibrium in idiopathic pulmonary fibrosis pathogenesis. Inflammation, 43, 1-7.]

12. [Margaritopoulos, G. A., Trachalaki, A., Wells, A. U., Vasarmidi, E., Bibaki, E., Papastratigakis, G., ... & Antoniou, K. M. (2018). Pirfenidone improves survival in IPF: results from a real-life study. BMC pulmonary medicine, 18, 1-7.
13. Fisher, M., Nathan, S. D., Hill, C., Marshall, J., Dejonckheere, F., Thuresson, P. O., & Maher, T. M. (2017). Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. Journal of managed care & specialty pharmacy, 23(3-b Suppl), S17-S24.
14. Lancaster, L. H., de Andrade, J. A., Zibrak, J. D., Padilla, M. L., Albera, C., Nathan, S. D., ... & Costabel, U. (2017). Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. European respiratory review, 26(146).
15. Reck, M. (2015). Nintedanib: examining the development and mechanism of action of a novel triple angiokinase inhibitor. Expert Review of Anticancer Therapy, 15(5), 579-594.
16. Roth, G. J., Binder, R., Colbatzky, F., Dallinger, C., Schlenker-Herceg, R., Hilberg, F., ... & Kaiser, R. (2015). Nintedanib: from discovery to the clinic. Journal of medicinal chemistry, 58(3), 1053-1063.
17. Wollin, L., Wex, E., Pautsch, A., Schnapp, G., Hostettler, K. E., Stowasser, S., & Kolb, M. (2015). Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. European Respiratory Journal, 45(5), 1434-1445.]
18. Tzouvelekis, A., Karampitsakos, T., Ntolios, P., Tzilas, V., Bouros, E., Markozannes, E., ... & Bouros, D. (2017). Longitudinal "real-world" outcomes of pirfenidone in idiopathic pulmonary fibrosis in Greece. Frontiers in medicine, 4, 213.
19. Salih, G. N., Shaker, S. B., Madsen, H. D., & Bendstrup, E. (2016). Pirfenidone treatment in idiopathic pulmonary fibrosis: nationwide Danish results. European clinical respiratory journal, 3(1), 32608.]
20. Thong Wan Yin, L., Bowen, B., & Henry, M. (2021). Real-life data on the safety and tolerability of Pirfenidone versus Nintedanib in Idiopathic Pulmonary Fibrosis (IPF) patients: A single-centre retrospective study. Idiopathic interstitial pneumonias.
21. Harari, S., Caminati, A., Albera, C., Vancheri, C., Poletti, V., Pesci, A., ... & Confalonieri, M. (2015). Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respiratory Medicine, 109(7), 904-913.
22. Hughes, G., Toellner, H., Morris, H., Leonard, C., & Chaudhuri, N. (2016). Real world experiences: pirfenidone and nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. Journal of clinical medicine, 5(9), 78.
23. Aiello, M., Bertorelli, G., Bocchino, M., Chetta, A., Fiore-Donati, A., Fois, A., ... & Sanduzzi, A. (2017). The earlier, the better: impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis. Pulmonary Pharmacology & Therapeutics, 44, 7-15.
24. Fernández-Fabrellas, E., Molina-Molina, M., Soriano, J. B., Portal, J. A. R., Ancochea, J., Valenzuela, C., et al. (2019). Demographic and clinical profile of idiopathic pulmonary fibrosis patients in Spain: the SEPAR national registry. Respir. Res. 20:127.
25. Tran, T., Šterclová, M., Mogulkoc, N., Lewandowska, K., Müller, V., Hájková, M., ... & Vašáková, M. (2020). The European MultiPartner IPF registry (EMPIRE): validating long-term prognostic factors in idiopathic pulmonary fibrosis. Respiratory research, 21, 1-9.
26. Bonella, F., Kreuter, M., Hagmeyer, L., Neurohr, C., Keller, C., Kohlhaeufl, M. J., ... & German Nintedanib Compassionate Use Consortium. (2016). Insights from the German compassionate use program of nintedanib for the treatment of idiopathic pulmonary fibrosis. Respiration, 92(2), 98-106
27. Ruaro, B., Gandin, I., Pozzan, R., Tavano, S., Bozzi, C., Hughes, M., Kodric, M., Cifaldi, R., Lerda, S., Confalonieri, M., Baratella, E., Confalonieri, P., & Salton, F. (2023). Nintedanib in Idiopathic Pulmonary Fibrosis: Tolerability and Safety in a Real Life Experience in a Single Centre in Patients also Treated with Oral Anticoagulant Therapy. Pharmaceuticals (Basel, Switzerland), 16(2), 307. https://doi.org/10.3390/ph16020307
28. Vietri, L., Cameli, P., Perruzza, M., Cekorja, B., Bergantini, L., d'Alessandro, M., ... & Bargagli, E. (2020). Pirfenidone in idiopathic pulmonary fibrosis: real-life experience in the referral centre of Siena. Therapeutic advances in respiratory disease, 14, 1753466620906326.
29. Pitre, T., Mah, J., Helmeczi, W., Khalid, M. F., Cui, S., Zhang, M., ... & Zeraatkar, D. (2022). Medical treatments for idiopathic pulmonary fibrosis: a systematic review and network meta-analysis. Thorax, 77(12), 1243-1250.
30. Lancaster, L. H., de Andrade, J. A., Zibrak, J. D., Padilla, M. L., Albera, C., Nathan, S. D., ... & Costabel, U. (2017). Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. European respiratory review, 26(146).

31. Rodríguez-Portal, J. A. (2018). Efficacy and safety of nintedanib for the treatment of idiopathic pulmonary fibrosis: an update. Drugs in R&D, 18(1), 19-25.
32. Crestani, B., Kolb, M., Wallaert, B., Quaresma, M., Stansen, W., & Richeldi, L. (2017). M33 Long-term efficacy of nintedanib is maintained in patients with idiopathic pulmonary fibrosis (ipf) irrespective of dose: subgroup analysis of inpulsis-on. Thorax, 72, A255.
33. Richeldi, L., Costabel, U., Selman, M., Kim, D. S., Hansell, D. M., Nicholson, A. G., ... & du Bois, R. M. (2011). Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. New England Journal of Medicine, 365(12), 1079-1087.
34. Tzouvelekis, A., Karampitsakos, T., Kontou, M., Granitsas, A., Malliou, I., Anagnostopoulos, A., ... & Bouros, D. (2018). Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: a real-life observational study in Greece. Pulmonary pharmacology & therapeutics, 49, 61-66.