PACEK, Katarzyna, PIEKARSKA, Małgorzata, PIKULICKA, Agata, JEDLINA, Klaudia, SZULC, Izabela, KASPERSKI, Radosław, SWACHA, Weronika & MAKOWSKA, Karolina. Idiopathic pulmonary fibrosis - novel approach on future treatment. Journal of Education, Health and Sport. 2023;13(2):268-272. eISSN 2391-8306. DOI https://dx.doi.org/10.12775/JEHS.2023.13.02.039
https://apcz.umk.pl/JEHS/article/view/41034
https://zenodo.org/record/7510020

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 24.11.2022. Revised: 21.12.2022. Accepted: 06.01.2023.

Idiopathic pulmonary fibrosis – novel approach on future treatment

Katarzyna Pacek, ORCID: 0000-0001-6947-558X, kasia.pacek1@gmail.com, Centralny Szpital Kliniczny MSWiA w Warszawie, ul. Wołoska 137, 02-507 Warszawa
Małgorzata Piekarska, ORCID: 0000-0001-5055-4923, piekarska13@gmail.com, Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Al. Kraśnicka 100, 20-718 Lublin
Agata Pikulicka, ORCID: 0000-0003-1693-8127, agapikulicka@gmail.com, Szpital Solec, ul. Solec 93, 00-382, Warszawa
Klaudia Jedlina, ORCID: 0000-0002-2363-2620, klaudiajedlina@gmail.com, Centralny Szpital Kliniczny MSWiA w Warszawie, ul. Wołoska 137, 02-507 Warszawa,
Izabela Szulc, ORCID: 0000-0002-2262-6886, izabelaszulc4@gmail.com,Szpital Praski P.W. Przemienienia Pańskiego w Warszawie, aleja "Solidarności" 67, 03-401 Warszawa
Radosław Kasperski, ORCID: 0000-0002-7364-3205, r.kasperski95@gmail.com, Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Al. Kraśnicka 100, 20-718 Lublin
Weronika Swacha, ORICID: 0000-0002-1865-5967, weronka6@gmail.com, Mazowieckie Centrum Stomatologii w Warszawie, ul.Nowy Zjazd 1, 00-301 Warszawa
Karolina Makowska, ORCID: 0000-0001-5467-3137, makowska.karolinaa@gmail.com, Uniwersytet Medyczny w Lublinie, Aleje Racławickie 1, 20-059 Lublin

ABSTRACT

Introduction

Idiopathic pulmonary fibrosis (IPF) is a fatal pulmonary disease that leads to progressive fibrosis and extremely poor resaults.. Since the etiology is unknown, there are highly limited options of the IPF treatment. The researchers are trying to discover the most valuable targets, leading them to the agents registered in different conditions or not registered as any other treatment. This innovative approach can result in IPF being determined as not fatal.

Purpose

The purpose of our review is to present possible future treatment of idiopathic pulmonary fibrosis and point out the promising targets that could lead the researchers to the development of better IPF management.

Materials and methods

We have reviewed the literature from the PubMed database searching for clinical trials, meta analysis and randomized controlled trials from the past 5 years. The keywords we agreed on offered us the most informative articles and made us hope for the further development of our article.

Results

Our review shows that there are new targets that could significantly benefit IPF treatment. However, the means we presented in our review need more research to prove its safeness, effectiveness in slowing down the decline of the FVC, improving patients' physical efficiency, their saturation level and most importantly their ability to stop the continuous fibrosis of the lungs.

Conclusions

The only treatment registered for IPF are nintedanib and pirfenidone, but the researchers continue the exploration of new possible measures to improve the survival rate and quality of life of the patients suffering from this fatal disease.

Key words
idiopathic pulmonary fibrosis; pamrevlumab; lung transplantation; senotherapeutics; recombinant human pentraxin 2

INTRODUCTION AND PURPOSE

Idiopathic pulmonary fibrosis (IPF) is the most frequent interstitial lung disease. The incidence of this disease is up to 9 out of 100 000 people per year in Europe and North America regions [1]. The survival rate of patients without antifibrotic therapy is extremely poor. The median of survivability for people affected by this specific interstitial lung disease is 3,2 years [2,3]. IPF is characterized by chronic, progressive pulmonary inflammation leading to fibrosis that is strictly limited to lungs. Unfortunately, this process is irreversible. The etiology is still unknown, although plenty of researchers are involved in discovering the IPF cause [4].This disease significantly reduces life expectancy alongside forced vital capacity (FVC)[5]. It is known that around 20% of IPF cases in Europe are familial (FIP) [6]. The studies have shown that polymorphism of MUC58 (rs35705950) gene can lead to a higher risk of both IPF and FIP [7], although polymorphism of the surfactant proteins genes (SFTPA and SFTPC), genes associated with telomerase (hTERT, TERC, RTEL1, PARN) and TOLLIP protein gene are also responsible for the development of FIP[8].

DIAGNOSIS

Ordinarily there are no manifestations that would indicate IPF during the physical examination. The patients often report exertional dyspnea as a major problem. While examining the patient, the doctors usually points out considerable inspiratory crackles mostly located in lower segments of the lungs. At times the crackles can occur all over the respiratory field. Clubbing of the fingers may also appear and is a sign of prolonged hypoxia. These symptoms are not specific to IPF and can lead to misdiagnosing patients with cardiac failure, elongation of the diagnosis and incorrect treatment [4,9]. There are three main diagnostic criteria for IPF. The first one is of huge value because it depends on excluding any known causes of interstitial lung diseases. As was said before, IPF has no known etiology. The second criterion is a specific pattern in chest imaging - high-resolution computed tomography (HRCT), which gives us the best image to diagnose interstitial diseases. The third criterion is a combination of HRCT patterns and histopathological patterns from lung biopsy. Laboratory testing is also not specific and is not recommended as standard practice [9,10].

MONITORING

The FVC supervision is important to confirm disease progression (if FVC decline is equal or greater than 10%). However, stable FVC does not reflect on remission of the disease. There are no other reliable monitoring criteria of IPF tendency. Moreover there are no other biomarkers of this disease. The further research of these is in urgent need [11,12].

STATE OF KNOWLEDGE

What we already know

It is exceptionally important to treat patients with IPF multidimensionally. That includes both pharmacotherapy and focusing on relieving the symptoms. Oxygen therapy is crucial to maintain or even improve patients' exercise tolerance and more importantly mitigate their dyspnea [13]. Although supportive care of the patients is a top priority, the disease-modifying drugs are nonexpendable to cure or at least slower the progression of IPF. We can mark out the only two antifibrotics that are currently approved in the IPF treatment. The first one is nintedanib. It's a tyrosine kinase inhibitor (VEGF, FGF and PDGF receptors) [5] that has been proven to minify forced vital capacity (FVC) reduction [14]. The other drug, pirfenidone is said to present anti-inflammatory, antifibrotic and antioxidant qualities equaling in improving patients' vital capacity (VC) [15,16]. Vital Capacity and Forced vital capacity are considered to be great indicators of survival and mortality in people affected by IPF, since they picture lung function [15].
It is very important to remember the variety of groups of drugs, as well as their combinations that can lead to a further progression of the IPF, but also can trigger exacerbation of the patients. It is necessary to point out the linkage of some medications that are proved to act oppositely to their main goal. The example of such activity can be the combination of prednisone, azathioprine and N-acetylcysteine. It has been found to be harmful, increase the death ratio compared to the patients in the control group and is a warning for other researchers and physicians[17].

New promising ways of treatment

- **Senotherapeutics**
  One of few examples of new ways of IPF treatment are the so called senolytics. Those drugs induce programmed cell death of the outdated cells, the accumulation of which is responsible for IPF development [18]. Those cells produce pro-apoptotic factors, although they can withstand apoptosis. The researchers from the United States conducted a first study on humans involving the effect of the senolytics on patients with stable IPF. They targeted the SCAPs (senescent cell anti-apoptotic pathways) and opted for therapeutics that

would only affect human senescent cells, not inducing apoptosis of non-senescent cultured ones. The agents of their choice occurred to be Dasatinib (D) and Quercetin (Q). The D and Q hybrid are said to exclusively induce apoptosis of the senescent cells. This study shows the possibility of alleviating patients' physical activity and function of the lungs in executed lung function tests [19,20].

- **Senomorphics**
  Those agents are based on senescent cell function regulation. The difference between senomorphics and senolytics is the fact that they don't lead to cells' apoptosis. The research conducted on rodents has shown that this group of therapeutics aims for molecules (e.g. IL-6, leukotrienes, TGF-β) and pathways (e.g. JAK-STAT) leading to the alleviation of lung fibrosis [21,20].

- **Anti-connective tissue growth factor therapy - Pamrevlumab**
- The trial published in 2019 has proven the effectiveness of pamrevlumab. The scientists have decided on a double-blind attempt with 30 mg/kg of the agent administered to patients for 48 weeks. The results demonstrated that pamrevlumab has relevantly improved lung function (the decrease in FVC has been reduced) as well as mitigate IPF development [22]. Pamrevlumab is also considered to be an agent that could overtake nintedanib's and pirfenidone's results in lung function improvement [23].

- **Recombinant human pentraxin 2 - PRM-151**
- The other name of this agent is purified serum amyloid P. Its main function is to suppress the formation of fibrocytes from monocytes. Fibrocytes take an active part in wound healing. Their profibrotic activity suggests a new way of IPF treatment by reducing their population [24]. Recombinant human pentraxin 2 has been proved to mitigate the VC decline comparatively to the placebo which gives us hope for further studies on this agent. Patients administered pentraxin did better in the 6-minute walk test as well. It is also worth mentioning that this protein had a positive impact on patients' cough, fatigue and nosopharyngitis [25,26].

- **Lysophosphatidic acid receptor (LPA1) antagonists**
- LPA1 mediates fibroblasts recruitment which is responsible for fibroblasts recruitment. An IPF treatment target - LPA1 antagonists have been proved to mitigate FVC decline, a crucial step in the future of IPF treatment. There are two LPA1 antagonists that underwent trials - BMS-986020 and bms-986278. Both of them are a promising future treatment for fatal lung fibrosis progression [27,28].

- **Drugs inhalation**
- Study conducted in 2018 has shown the possibility of embracing inhalatory drugs in IPF treatment. The researchers have proven that radiolabelled salbutamol in aerosol can access peripheral lung fields which equals a new potential way of delivering drugs directly into bronchioles, where fibrosis begins. That could help to skip contingent effects of drugs administered orally. The effectiveness of this method is yet to be proven with IPF registered medications[29].

- **Pulmonary rehabilitation (PR)**
- Regular pulmonary rehabilitation is said to visibly improve patients' quality of life besides their FVC. Further studies are in urgent need to decide on PR's assets and compare them to it's flaws in order to measure safeness of this treatment method [30].

- **Tele-rehabilitation**
  The randomized trial conducted on IPF patients have shown the benefits of regular rehabilitation. Patients could exercise in a moment suitable for them which made it easier for them to be consistent. The test results were: significant improvement of patients satisfaction as well as their exercise capacity. Unfortunately, the pedometry and quality of life did not improve [31].

- **Lung transplantation**
- Besides all researchers' attempts to cure IPF with pharmacological substances, there is hopefulness in the surgical approach. The studies have shown that lung transplantation - of a single lung as well as both of them - may be more beneficial than any other treatment. The main asset of this method is definitely improvement of the patients' symptoms, although it is possible to achieve that by pharmacological treatment [11]. We cannot forget about the most important value - the patients' survival rate, which is the main quality advocating the lung transplant over any accessible treatment. Single lung transplant (SLT) may not sound as worthwhile as the double lung transplant (DLT) , although it has proved to yield longer survival time. Moreover the patients under 65 years old turned out to have a better outcome of lung transplant . It is also worth mentioning that pulmonary hypertension over 30 mmHg and saturation under 80% are said to decrease the survival time[32].

SUMMARY

The disease with unknown etiology can be a huge dilemma when it comes to the treatment. Many years of research can

often bring little findings. That is why it is crucial to continue studies on IPF and possible targets for the remedies and help the patients improve their quality of life and give hope for the future. Senotherapeutics, senolytics, pamrevlumab, recombinant human pentraxin 2, lysophosphatidic acid receptor antagonists, the inhalation of medicaments, pulmonary rehabilitation and lung transplant have high probability of becoming registered as IPF treatments in the future, if the research continues. Nonetheless it is important to continue the studies on new targets and methods that can improve patients' survival outcomes and the quality of their lives.

Bibliography:

[1]Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015; 46: 795–806. doi: 10.1183/09031936.00185114

[2] Khor YH, Ng Y, Barnes H, Goh NSL, McDonald CF, Holland AE. Prognosis of idiopathic pulmonary fibrosis without anti-fibrotic therapy: a systematic review. Eur Respir Rev. 2020 Aug 4;29(157):190158. doi: 10.1183/16000617.0158-2019. PMID: 32759374; PMCID: PMC9488716.

[3]Ryerson CJ, Kolb M. The increasing mortality of idiopathic pulmonary fibrosis: fact or fallacy? *Eur Respir J* 2018; 51: 1702420. doi: 10.1183/13993003.02420-2017

[4] Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018 May 10;378(19):1811-1823. doi: 10.1056/NEJMra1705751. PMID: 29742380.

[5]Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2071-82. doi: 10.1056/NEJMoa1402584. Epub 2014 May 18. Erratum in: N Engl J Med. 2015 Aug 20;373(8):782. PMID: 24836310.

[6] Interna Szczeklika 2022. / [red.prow.] Piotr Gajewski [Wyd.13]. Kraków: Wydawnictwo Medycyna Praktyczna, 2022

[7]Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011 Apr 21;364(16):1503-12. doi: 10.1056/NEJMoa1013660. PMID: 21506741; PMCID: PMC3379886.

[8]Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al.. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007 Mar 29;356(13):1317-26. doi: 10.1056/NEJMoa066157. PMID: 17392301.

[9] Wakwaya Y, Brown KK. Idiopathic Pulmonary Fibrosis: Epidemiology, Diagnosis and Outcomes. Am J Med Sci. 2019 May;357(5):359-369. doi: 10.1016/j.amjms.2019.02.013. Epub 2019 Feb 15. PMID: 31010461.

[10] Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al.; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68. doi: 10.1164/rccm.201807-1255ST. PMID: 30168753.

[11] Glass DS, Grossfeld D, Renna HA, Agarwala P, Spiegler P, DeLeon J, et al. Idiopathic pulmonary fibrosis: Current and future treatment. Clin Respir J. 2022 Feb;16(2):84-96. doi: 10.1111/crj.13466. Epub 2022 Jan 10. PMID: 35001525; PMCID: PMC9060042.

[12] Wuyts, W. A., Wijsenbeek, M., Bondue, B., Bouros, D., Bresser, P., Robalo Cordeiro, C., … Bendstrup, E. (2019). Idiopathic Pulmonary Fibrosis: Best Practice in Monitoring and Managing a Relentless Fibrotic Disease. Respiration, 99(1), 73–82. doi:10.1159/000504763

[13] Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, et al. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. Respirology. 2017 Jul;22(5):957-964. doi: 10.1111/resp.13002. Epub 2017 Feb 22. PMID: 28225205.

[14]Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008 Jun 15;68(12):4774-82. doi: 10.1158/0008-5472.CAN-07-6307. PMID: 18559524.

[15] Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010 Apr;35(4):821-9. doi: 10.1183/09031936.00005209. Epub 2009 Dec 8. PMID: 19996196.

[16] Chaudhary NI, Roth GJ, Hilberg F, Müller-Quernheim J, Prasse A, Zissel G, et al.. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J. 2007 May;29(5):976-85. doi: 10.1183/09031936.00152106. Epub 2007 Feb 14. PMID: 17301095.

[17] Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354. Epub 2012 May 20. PMID: 22607134; PMCID: PMC3422642.

[18] Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, et al. Cellular senescence mediates fibrotic pulmonary disease. Nat Commun. 2017 Feb 23;8:14532. doi: 10.1038/ncomms14532. PMID: 28230051; PMCID: PMC5331226.

[19] Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine. 2019 Feb;40:554-563. doi: 10.1016/j.ebiom.2018.12.052. Epub 2019 Jan 5. PMID: 30616998; PMCID: PMC6412088.

[20]Kim EC, Kim JR. Senotherapeutics: emerging strategy for healthy aging and age-related disease. BMB Rep. 2019 Jan;52(1):47-55. doi: 10.5483/BMBRep.2019.52.1.293. PMID: 30526770; PMCID: PMC6386227.

[21] Merkt W, Bueno M, Mora AL, Lagares D. Senotherapeutics: Targeting senescence in idiopathic pulmonary fibrosis. Semin Cell Dev Biol. 2020 May;101:104-110. doi: 10.1016/j.semcdb.2019.12.008. Epub 2019 Dec 24. PMID: 31879264; PMCID: PMC7913053.
[22] Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, et al. Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2020 Jan;8(1):25-33. doi: 10.1016/S2213-2600(19)30262-0. Epub 2019 Sep 28. PMID: 31575509.
[23] Di Martino E, Provenzani A, Vitulo P, Polidori P. Systematic Review and Meta-analysis of Pirfenidone, Nintedanib, and Pamrevlumab for the Treatment of Idiopathic Pulmonary Fibrosis. Ann Pharmacother. 2021 Jun;55(6):723-731. doi: 10.1177/1060028020964451. Epub 2020 Oct 15. PMID: 33054319.
[24] Naik-Mathuria B, Pilling D, Crawford JR, Gay AN, Smith CW, Gomer RH, et al. Serum amyloid P inhibits dermal wound healing. Wound Repair Regen. 2008 Mar-Apr;16(2):266-73. doi: 10.1111/j.1524-475X.2008.00366.x. PMID: 18318811; PMCID: PMC2908397.
[25]Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, et al. Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis: A Randomized Clinical Trial. JAMA. 2018 Jun 12;319(22):2299-2307. doi: 10.1001/jama.2018.6129. PMID: 29800034; PMCID: PMC6134440.
[26] Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, et al. Long-term treatment with recombinant human pentraxin 2 protein in patients with idiopathic pulmonary fibrosis: an open-label extension study. Lancet Respir Med. 2019 Aug;7(8):657-664. doi: 10.1016/S2213-2600(19)30172-9. Epub 2019 May 20. PMID: 31122893.
[27] Palmer SM, Snyder L, Todd JL, Soule B, Christian R, Anstrom K, et al. Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial of BMS-986020, a Lysophosphatidic Acid Receptor Antagonist for the Treatment of Idiopathic Pulmonary Fibrosis. Chest. 2018 Nov;154(5):1061-1069. doi: 10.1016/j.chest.2018.08.1058. Epub 2018 Sep 7. PMID: 30201408.
[28] Corte TJ, Lancaster L, Swigris JJ, Maher TM, Goldin JG, Palmer SM, et al. Phase 2 trial design of BMS-986278, a lysophosphatidic acid receptor 1 (LPA1) antagonist, in patients with idiopathic pulmonary fibrosis (IPF) or progressive fibrotic interstitial lung disease (PF-ILD). BMJ Open Respir Res. 2021 Dec;8(1):e001026. doi: 10.1136/bmjresp-2021-001026. PMID: 34969771; PMCID: PMC8718498.
[29] Usmani OS, Biddiscombe MF, Yang S, Meah S, Oballa E, Simpson JK, et al. The topical study of inhaled drug (salbutamol) delivery in idiopathic pulmonary fibrosis. Respir Res. 2018 Feb 6;19(1):25. doi: 10.1186/s12931-018-0732-0. PMID: 29409488; PMCID: PMC5801831.
[30]Yu X, Li X, Wang L, Liu R, Xie Y, Li S, Li J. Pulmonary Rehabilitation for Exercise Tolerance and Quality of Life in IPF Patients: A Systematic Review and Meta-Analysis. Biomed Res Int. 2019 Mar 21;2019:8498603. doi: 10.1155/2019/8498603. PMID: 31016200; PMCID: PMC6448340.
[31] Cerdán-de-Las-Heras J, Balbino F, Løkke A, Catalán-Matamoros D, Hilberg O, Bendstrup E. Tele-Rehabilitation Program in Idiopathic Pulmonary Fibrosis-A Single-Center Randomized Trial. Int J Environ Res Public Health. 2021 Sep 23;18(19):10016. doi: 10.3390/ijerph181910016. PMID: 34639313; PMCID: PMC8508000.
[32] Amor MS, Rosengarten D, Shitenberg D, Pertzov B, Shostak Y, Kramer MR. Lung Transplantation in Idiopathic Pulmonary Fibrosis: Risk Factors and Outcome. Isr Med Assoc J. 2020 Dec;22(12):741-746. PMID: 33381944.