ANTIFIBROTIC FOR TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

Executive Summary

[Adapted from the report by ROZA SARIMIN]

Review Group Membership

MaHTAS Reviewer:
Dr. Roza Sarimin
Dr. Izzuna Mudla Mohamed Ghazali

External Reviewer:
Dr. Irfhan Ali Hyder Ali
Dr. Syazatul Syakirin Sirol Aflah
Dr. Tie Siew Teck

For further information please contact:

Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya.

Tel: 603 8883 1246

Fax: 603 8883 1230

Available at the following website:
http://www.moh.gov.my

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a devastating, rapidly fatal lung disease with considerable impact on patients and carers as the disease progresses, characterised by progressive fibrosis of lung interstitium, decreased lung volume and pulmonary insufficiency, with a median survival of three to five years from diagnosis. The condition is more common in males with advancing age. Idiopathic pulmonary fibrosis is classified as a rare disease, designated as an orphan indication by the European Medicines Agency. An annual incidence of three to nine cases per 100,000 population for Europe were reported. In Malaysia, 54 IPF cases were reported from January 2017 to June 2019 in a single centre. A total of 124 patients with IPF were reported from three centers from 2017 to September 2020.Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. Early and accurate diagnosis is important for a better outcome. While IPF is ultimately fatal, its clinical course is variable and unpredictable, with some patients experiencing a rapid decline in lung function while others progress much more slowly. Prompt treatment of IPF is crucial to preserve individuals' lung function, reducing the risk of acute exacerbations and improving outcomes.

Conventional medication for patients with IPF included glucocorticosteroids or immunosuppressants. N-acetylcysteine and triple therapy (N-acetylcysteine, prednisolone and azathioprine) are not recommended but still being used in clinical practice. The triple therapy was shown to increase the rate of mortality and hospitalisation compared with placebo. Advances in the management of this disease has been transformed with two disease-modifying therapies have been approved in the US, Europe and many other countries, nintedanib and pirfenidone. Nintedanib and pirfenidone were granted orphan drug designation for treatment of rare disease. However, it has been reported that high treatment cost was involved in the use of antifibrotic for treating IPF. No prescription criteria available in selecting different type of antifibrotic to these patients. Earlier, pirfenidone and nintedanib were reported as not registered in the Ministry of Health (MOH) formulary, and needed Director General of Health approval on a case by case basis. However, recently in November 2019 Nintedanib was listed in the MOH drug formulary while Pirfenidone still requires Director General of Health approval on a case by case basis. Hence, this technology review was conducted following a request from the former head of Respiratory Services, Ministry of Health Malaysia to review the available best scientific evidence on antifibrotic therapy as an available option for patients with IPF in Malaysia.

Objective/Aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of antifibrotic therapy for the treatment of patients with idiopathic pulmonary fibrosis.

Results and Conclusions

Effectiveness

Based on the above review, there was sufficient good level of evidences on pirfenidone and nintedanib to be used in the treatment of patients with IPF. Evidence demonstrated that pirfenidone and nintedanib were effective in improving FVC from baseline and slowing rate of FVC decline, compared to placebo in adult patients with IPF. Pirfenidone was effective in lowering risk of decline in percent predicted FVC of ≥10% over one year, compared to placebo in these patients.

- In patients with IPF, pirfenidone and nintedanib showed improvement in FVC from baseline, compared to placebo after one year [pirfenidone versus

placebo, mean difference (MD) was 0.12 litre (L) (95%credible interval (CrI) 0.03, 0.22 L), and nintedanib versus placebo, MD was 0.11 L (95%CrI 0.00, 0.22L).

- Both pirfenidone and nintedanib significantly slowed the rate of FVC decline compared to placebo (OR 0.62, 95%CrI 0.52, 0.74) and OR 0.4 (95%CrI 0.34, 0.51) respectively.
- Patients treated with pirfenidone had lower risk of experiencing a decline in percent predicted FVC of ≥10% over one year (OR=0.58, 95%CrI 0.40, 0.88) whereas there was no significant difference between nintedanib and placebo (OR=0.65, 95%CrI 0.42, 1.02).

Pirfenidone demonstrated treatment benefit for mortality outcomes (all-cause and other mortality outcomes; IPF-related mortality, treatment-emergent all-cause mortality, and treatment-emergent IPF-related mortality), progression free survival (reduce risk of disease progression at one year), change from baseline to one year in six-minute walk distance(6MWD)(reducing proportion of patients with a ≥ 50m decline in 6MWD) and dyspnoea (fewer patients in the pirfenidone group experienced a ≥ 20-point increase in the UCSD SOBQ score or death at one year), compared with placebo.

Nintedanib demonstrated benefit in reducing rate of acute exacerbation compared to placebo.

Safety

Pirfenidone was approved by the European Medicines Agency for the treatment of mild-to-moderate idiopathic pulmonary fibrosis, approved in several countries (Japan,India, China, United States). Nintedanib was approved by the United States Food and Drug Administration for use in IPF, and approved in the EU, Canada, Japan, Switzerland, and few other countries. Long term treatment with pirfenidone or nintedanib was reported as safe and generally well tolerated with gastrointestinal and skin related events were commonly reported adverse events following pirfenidone, of which were mostly mild to moderate, while diarrhoea is the most common adverse event reported following nintedanib use.

Economic evaluation/cost-effectiveness analysis

In a cost-effectiveness analysis conducted in UK, the ICER ranged from £132,658 to £145,310 per QALY gained for nintedanib and £172,198 to £190,146 per QALY gained for pirfenidone, compared with BSC. In the base case deterministic pairwise comparison with pirfenidone, nintedanib was found to have fewer acute exacerbations and resulted in less cost and more QALY gained. The cost effectiveness acceptability curve showed nintedanib dominates pirfenidone at any threshold level. Adequate informed consent should be obtained prior pirfenidone or nintedanib administration, and sufficient education to patients is required. In Malaysia, a total of 124 patients with IPF were reported since 2017 to September 2020 from three centers (National Respiratory Institute, Hospital Serdang and Hospital Taiping). Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. The number of mild or moderate IPR cases by year reported from these centers were 18(2017), 22(2018), 24(2019) and 16(2020), respectively with average of 20 cases reported per year. Estimated annual treatment cost of patients with IPF using pirfenidone is RM 50,880, and using nintedanib is RM42,000. Hence, considering this figures, estimated annual treatment cost of using nintedanib or pirfenidone is between RM840,000 to RM1,017,600 for mild or moderate IPF patients in Malaysia. However this estimation is limited by the unavailability of data on number of patients requiring pirfenidone such as those contraindicated to nintedanib

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2020), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2020), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020). The last search was conducted on 31 March 2020. Relevant articles were critically appraised and evidence graded using US / Canadian Preventive Services Task Force.