EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Real world experience of nintedanib for progressive fibrosing interstitial lung disease in the UK

Journal:	*European Respiratory Journal*
Manuscript ID	ERJ-01132-2023
Manuscript Type:	Original Research Article
Date Submitted by the Author:	05-Jul-2023
Complete List of Authors:	Dixon, Giles; University of Exeter, Department of Clinical & Biomedical Sciences; North Bristol NHS Trust, Bristol Interstitial Lung Disease Service, ; Royal Devon University Healthcare NHS Foundation Trust, South West Peninsula ILD Network; Royal United Hospital Hague, Samuel; North Bristol NHS Trust, Bristol Interstitial Lung Disease Service Mulholland, Sarah; North Bristol NHS Trust, Bristol Interstitial Lung Disease Service Khin, Aye Myat Noe; Royal Devon University Healthcare NHS Foundation Trust, South West Peninsula ILD Network Thould, Hannah; Royal Devon University Healthcare NHS Foundation Trust, South West Peninsula ILD Network Connon, Roisin; Antrim Area Hospital, Northern Health and Social Care Trust, Antrim, Northern Ireland, UK Minnis, Paul; Antrim Area Hospital, Northern Health and Social Care Trust, Antrim, Northern Ireland, UK Murtagh, Eoin; Antrim Area Hospital, Northern Health and Social Care Trust, Antrim, Northern Ireland, UK Khan, Fasihul; Glenfield Hospital, University Hospitals of Leicester NHS Trust Toor, Sameen; Glenfield Hospital, University Hospitals of Leicester NHS Trust Lawrence, Alexandra; Guy's and St Thomas' NHS Foundation Trust Naqvi, Marium; Guy's and St Thomas' NHS Foundation Trust, West, Alex; Guy's and St Thomas' NHS Foundation Trust Coker, Robina; Imperial College Healthcare NHS Trust, Hammersmith Hospital Ward, Katie; Imperial College Healthcare NHS Trust, Hammersmith Hospital Yazbeck, Leda; Imperial College Healthcare NHS Trust, Hammersmith Hospital Hart, Simon; Hull University Teaching Hospitals NHS Trust Garfoot, Theresa; Manchester University NHS Foundation Trust, Interstitial Lung Disease Unit, Wythenshawe Hospital, Newman, Kate; Manchester University NHS Foundation Trust, Interstitial Lung Disease Unit, Wythenshawe Hospital, Rivera-Ortega, Pilar; Manchester University NHS Foundation Trust, Interstitial Lung Disease Unit, Wythenshawe Hospital, Stranks, Lachlan; Manchester University NHS Foundation Trust,

	Interstitial Lung Disease Unit, Wythenshawe Hospital, Beirne, Paul; Leeds Teaching Hospitals NHS Trust Bradley, Jessica; Leeds Teaching Hospitals NHS Trust Rowan, Catherine; Leeds Teaching Hospitals NHS Trust Agnew, Sarah; Liverpool University Hospitals NHS Foundation Trust, Liverpool Interstitial Lung Disease Service, Aintree Hospital Ahmad, Mahin; Liverpool University Hospitals NHS Foundation Trust, Liverpool Interstitial Lung Disease Service, Aintree Hospital Spencer, Lisa; Liverpool University Hospitals NHS Foundation Trust, Liverpool Interstitial Lung Disease Service, Aintree Hospital Aigbirior, Joshua; Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital Fahim, Ahmed; Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital Wilson, Andrew; University of East Anglia, Norwich Medical School, ; Norfolk and Norwich University Hospitals NHS Foundation Trust Butcher, Elizabeth; Nottingham University Hospitals NHS Trust Chong, Sy Giin ; Nottingham University Hospitals NHS Trust Saini, Gauri; Nottingham University Hospitals NHS Trust Zulfikar, Sabrina; Oxford University Hospitals NHS Foundation Trust Chua, Felix; Royal Brompton & Harefield NHS Foundation Trust George, Peter; Royal Brompton & Harefield NHS Foundation Trust Kokosi, Maria; Royal Brompton & Harefield NHS Foundation Trust Kouranos, Vasileios; Royal Brompton & Harefield NHS Foundation Trust Molyneaux, Phillip; Royal Brompton & Harefield NHS Foundation Trust, Renzoni, Elisabetta; Royal Brompton & Harefield NHS Foundation Trust Vitri, Benedetta; Royal Brompton & Harefield NHS Foundation Trust Wells, Athol; Royal Brompton & Harefield NHS Foundation Trust Nicol, Lisa; Royal Infirmary of Edinburgh, Respiratory Department Bianchi, Stephen; Sheffield Teaching Hospitals NHS Foundation Trust Kular, Raman; Sheffield Teaching Hospitals NHS Foundation Trust Liu, HuaJian; Southern Health and Social Care Trust John, Alexander; Southern Health and Social Care Trust Barth, Sarah; Imperial College Healthcare NHS Trust, St Mary's Hospital Wickremasinghe, Melissa; Imperial College Healthcare NHS Trust, St Mary's Hospital Forrest, Ian; Newcastle Upon Tyne Hospitals NHS Foundation Trust Grimes, Ian; Newcastle Upon Tyne Hospitals NHS Foundation Trust Simpson, A. John ; Newcastle University; Newcastle Upon Tyne Hospitals NHS Foundation Trust Fletcher, Sophie; University Hospital Southampton NHS Foundation Trust; University of Southampton, NIHR Southampton Respiratory Biomedical Research Centre and School of Clinical and Experimental Sciences, Faulty of Medicine, Jones, Mark; University Hospital Southampton NHS Foundation Trust; University of Southampton, NIHR Southampton Respiratory Biomedical Research Centre and School of Clinical and Experimental Sciences, Faulty of Medicine, Kinsella, Emma; University Hospital Southampton NHS Foundation Trust Naftel, Jennifer; University Hospital Southampton NHS Foundation Trust Wood, Nicola; University Hospital Southampton NHS Foundation Trust Chalmers, Jodie; University Hospitals Birmingham NHS Foundation Trust Crawshaw, Anjali; University Hospitals Birmingham NHS Foundation Trust Crowley, Louise; University Hospitals Birmingham NHS Foundation Trust Dosanjh, Davinder; University Hospitals Birmingham NHS Foundation Trust Huntley, Christopher; University Hospitals Birmingham NHS Foundation Trust; University of Birmingham Institute of Applied Health Research, Walters, Gareth; University Hospitals Birmingham NHS Foundation Trust; University of Birmingham Institute of Applied Health Research,

	Gatheral, Timothy; University Hospitals of Morecambe Bay NHS Foundation Trust, Lancashire and South Cumbria ILD service Plum, Catherine; University Hospitals of Morecambe Bay NHS Foundation Trust, Lancashire and South Cumbria ILD service Bikmalla, Shiva; University Hospitals of North Midlands NHS Trust Muthusami, Raja; University Hospitals of North Midlands NHS Trust Stone , Helen; University Hospitals of North Midlands NHS Trust Rodrigues, Jonathan; Royal United Hospitals Bath NHS Foundation Trust; University of Bath, Department of Health Tsaneva-Atanasova, Krasimira; University of Exeter, Department of Mathematics and Statistics, Faculty of Environment, Science and Economy; University of Exeter, EPSRC Hub for Quantitative Modelling in Healthcare; University of Exeter, Living Systems Institute Scotton, Chris; University of Exeter, Department of Clinical & Biomedical Sciences Gibbons, Michael; University of Exeter, Department of Clinical & Biomedical Sciences; Royal Devon University Healthcare NHS Foundation Trust, South West Peninsula ILD Network Barratt, Shaney; North Bristol NHS Trust, Bristol Interstitital Lung Disease Service ; University of Bristol School of Clinical Science,
Key Words:	interstitial lung disease, pulmonary fibrosis
Abstract:	Background Nintedanib slows progression of lung function decline in patients with progressive fibrosing interstitial lung disease (PF-ILD) and was recommended for this indication within the NHS in Scotland in June 2021 and in England, Wales and Northern Ireland in November 2021. To date there has been no national evaluation of the use of nintedanib for PF-ILD in a real-world setting. Methods Twenty-six UK centres were invited to take part in a national service evaluation between 17/11/21 and 30/09/22. Summary data regarding underlying diagnosis, pulmonary function tests, diagnostic criteria, radiological appearance, concurrent immunosuppressive therapy and drug tolerability was collected via electronic survey. Results Twenty-four UK prescribing centres responded to the service evaluation invitation. Between 17/11/2021 and 30/09/2022, 1120 patients received a multi-disciplinary team recommendation to commence nintedanib for PF-ILD. The most common underlying diagnoses were hypersensitivity pneumonitis (298/1120,26.6%), connective tissue disease associated interstitial lung disease (197/1120,17.6%), rheumatoid arthritis associated ILD (180/1120,16.0%), idiopathic non-specific interstitial pneumonia (125/1120,11.1%) and unclassifiable ILD (100/1120,8.9%). Of these, 54.4% (609/1120) were receiving concomitant corticosteroids, 355/1120 (31.7%) were receiving concomitant mycophenolate mofetil and 340/1120 (30.3%) were receiving another immunosuppressive/modulatory therapy. Radiological progression of ILD combined with worsening respiratory symptoms was the most common reason for the diagnosis of PF-ILD. Conclusion We have demonstrated the use of nintedanib for the treatment of PFILD across a broad range of underlying conditions. Nintedanib is frequently co-prescribed alongside immunosuppressive and immunomodulatory

	therapy. The use of nintedanib for the treatment of PF-ILD has demonstrated acceptable tolerability in a real-world setting.

Real world experience of nintedanib for progressive fibrosing interstitial lung disease in the UK

Introduction

Progressive fibrosing interstitial lung disease (PF-ILD) describes a cohort of patients who develop disease progression despite optimal pharmacotherapy.[1] It is characterised by a combination of worsening respiratory symptoms, declining lung function and increasing extent of fibrosis on high-resolution computed tomography (HRCT). PF-ILD is observed in a wide range of fibrosing ILDs including connective tissue disease associated ILD (CTD-ILD), hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia (NSIP), and unclassifiable ILD.[1] The clinico-phenotypical and mechanistic overlap between idiopathic pulmonary fibrosis (IPF) and PF-ILD allows the potential for a common treatment pathway.[1]

Estimations of the proportion of patients with fibrosing ILD who develop a progressive phenotype have historically varied and were reported to be between 13 - 53%.[2] Recently, a robust multi-centre Canadian prospective registry study has demonstrated progression in 39-59% of patients with fibrosing ILD despite conventional therapy dependent on disease subtype.[3]

The landmark INBUILD study demonstrated the efficacy of the anti-fibrotic tyrosine kinase inhibitor nintedanib in treating a wide range of fibrosing ILDs.[4] Nintedanib was shown to reduce the annual rate of lung function decline in patients with fibrosing ILD regardless of underlying subtype.[4-6] Nintedanib was approved by the National Institute of Health and Care Excellence (NICE) in November 2021 for use in PF-ILD. The NICE technology appraisal used the criteria established by the INBUILD study to define the prescribing criteria in England.[4]

Nintedanib is licensed for use in patients with fibrosing ILD which has progressed despite conventional therapy. Whilst the INBUILD study excluded the use of immunosuppression other than low dose prednisolone at baseline, evidence for the concomitant use of nintedanib and immunosuppression originates from the SENSCIS study of nintedanib in systemic sclerosis–ILD (SSc-ILD). The study included 279/576 (48.4%) participants who were receiving mycophenolate mofetil (MMF) at baseline.[6] Nintedanib reduced the annual rate of forced vital capacity (FVC) decline in participants both receiving and not receiving MMF, with no difference in adverse events.[7]

Data from a national early access programme in the UK demonstrated real-world efficacy of nintedanib in PF-ILD.[8] Despite the study cohort demonstrating a greater impairment in FVC and transfer capacity (DLCO) at baseline compared to INBUILD, nintedanib was still able to slow the rate of lung function decline.

The aim of this UK wide service evaluation was to document prescribing practices in the real world for the use of nintedanib for PF-ILD. We aimed to document the criteria used for PF-ILD diagnosis, the underlying disease subsets, the severity of disease at drug initiation and the concomitant use of immunosuppressive therapies.

Methods

Service evaluation

In England, anti-fibrotic medications are available through ILD specialist centres and through general hospitals in Scotland, Wales and Northern Ireland. 26 anti-fibrotic prescribing centres in the UK were

invited to service evaluation inclusion by email. Individual participating centres registered this project with their local healthcare trust service evaluation/audit departments, complying with Caldicott principles. No personal identifiable information was submitted for study. The study was not considered research by the UK Health Research Authority (HRA) decision tool and did not require HRA or ethical approval.

Data collection

Study centres completed a pre-defined survey for patients with a multi-disciplinary team (MDT) decision to commence nintedanib for non-IPF PF-ILD between 17/11/2021 and 30/09/22. A copy of the survey can be found in the supplementary material (Suppl 1.).

Data collected included underlying diagnosis, diagnostic criteria, concomitant therapy, radiological pattern, forced vital capacity (FVC) and transfer capacity (DLCO) at baseline and reason for drug discontinuation.

Summary data was grouped into categories prior to submission by individual participating centres. Individual-level patient data was not centrally collated.

Responses were collected by electronic survey (JISC Online surveys, UK) and collated by the coordinating centres (North Bristol NHS Trust and Royal Devon University Healthcare NHS Foundation Trust).

Progression criteria

The UK has adopted progression criteria defined by the INBUILD study.[4] All patients commenced upon nintedanib for PF-ILD are required to fulfil one of the following criteria:

i) A relative decline in FVC% predicted of at least 10% over the previous 24 months
ii) A relative decline in FVC% predicted of at least 5%, but less than 10%, with worsening respiratory symptoms
iii) A relative decline in FVC% predicted of at least 5%, but less than 10%, with increasing fibrotic changes on HRCT compared with the previous 24 months
iv) Worsening respiratory symptoms and increasing fibrotic changes on HRCT over the previous 24 months.

Results

Twenty-four (24/26, 92.3%) centres responded to the survey; participating centres can be found in the online supplementary material (Suppl 2). The number of patients prescribed nintedanib across specialist centres differed during the assessment period (7 – 129). In total, 1120 patients had an MDT recommendation to commence nintedanib for PF-ILD.

Treatment by subtype

Figure 1 demonstrates the subtypes of ILD for which nintedanib was prescribed. The most common subtypes were hypersensitivity pneumonitis (HP; 298/1120, 26.6%), rheumatoid arthritis related ILD (180/1120, 16.0%), idiopathic NSIP (125/1120, 11.2%) and unclassifiable ILD (100/1120, 8.9%). 72/1120 patients had criteria for diagnosis labelled as 'Other'. This included pleuroparenchymal

fibroelastosis (PPFE; 19/1120, 1.7%), other CTD-related ILD (11/1120, 1.0%), fibrotic organising pneumonia (7/1120, 0.6%), interstitial pneumonia with autoimmune features (IPAF; 6/1120, 0.5%) and asbestosis (5/1120, 0.4%).

PF-ILD criteria and radiological pattern

Figure 2 demonstrates the primary criteria by which PF-ILD was diagnosed in the cohort. 418/1120 (37.3%) were diagnosed based on progressive disease identified on high-resolution CT scan (HRCT) with progression of symptoms (Criteria 4). 281/1120 (25.1%) patients fulfilled >1 diagnostic criteria for nintedanib prescription.

The MDT consensus radiological patterns reported were definite usual interstitial pneumonia (UIP) pattern 252/1120 (22.5%), probable UIP 111/1120 (9.9%), indeterminate for UIP 53/1120 (4.7%), fibrotic HP 262/1120 (23.4%), fibrotic NSIP 261/1120 (23.3%) and alternative pattern 181/1120 (16.2%).

Concomitant therapy

Concomitant immunomodulatory therapy was commonly prescribed. 609/1120 (54.4%) patients were receiving oral corticosteroids at the time of commencing nintedanib. Mycophenolate mofetil was the most commonly co-prescribed immunosuppressive therapy after corticosteroids 335/1120 (29.9%). Table 1 demonstrates the range of immunomodulatory and immunosuppressive therapies that were intended to be continued alongside nintedanib.

Immunosuppressive or immunomodulatory therapy was stopped prior to commencing nintedanib in 21/1120 patients. The most commonly discontinued medications were MMF (8/21) and oral corticosteroids (5/21).

Pulmonary function at time of initiation

Baseline pulmonary function tests at the time of MDT decision to commence nintedanib for PF-ILD are demonstrated in Figure 3. The median percentage predicted forced vital capacity (FVC) category was ≥ 60 to <70% and median percentage predicted transfer capacity (DLCO) category was <40%. 181/1120 participants had no value for % predicted DLCO which represented patients with missing data or who were unable to perform DLCO testing.

Multi-disciplinary team

There were a range of prescribing healthcare professionals across and within prescribing centres. The healthcare professionals prescribing nintedanib were reported to be respiratory physicians (23/24), nurse specialists (14/24), specialist pharmacists (12/24), and rheumatologists (4/24).

Drug initiation and discontinuation

By 30/09/2022, 928/1120 (82.9%) patients had commenced nintedanib, the remaining patients were awaiting initiation. The proportion of patients awaiting drug initiation as of 30/09/2022 varied by prescribing centre, ranging from 42% to 100% of patients. 10/24 participating centres had initiated all intended patients on nintedanib by 30thSeptember 2022.

At the time of service evaluation submission, 175/928 (18.8%) participants had discontinued nintedanib. The most common reasons for nintedanib discontinuation were death (63/175, 36.0%), drug tolerability (83/175, 47.4%) and deranged liver function test (16/175, 9.1%).

Discussion

The service evaluation has demonstrated widespread uptake of the use of nintedanib for PF-ILD in the UK. The NICE Technology Appraisal Guidance predicted a total of 900 patients in the UK living with PF-ILD would be eligible for nintedanib.[9] This service evaluation has demonstrated that 1120 patients have had an MDT decision to commence nintedanib for PF-ILD between November 2021 and September 2022 and 928 had initiated treatment by 30/09/2022. This highlights the underestimation of the potentially eligible patients living with PF-ILD in the UK which has important implications for service provision.

The study highlights variation in the proportion of patients with an MDT decision to commence nintedanib and those who have initiated treatment. This variation could be explained by a combination of size of specialist centre, local referral patterns and the ability of individual centres to manage the increased demand for nintedanib initiation. Discrepancies in UK service provision have been highlighted by the 2021 Getting it Right First Time Report.[10] This report revealed variation in waiting times for clinical assessment, differences in medical workforce provision and variation in specialist nursing and pharmacy services. The prescription of nintedanib for PF-ILD in the UK was not permitted until 90 days following the NICE recommendation. This had the effect of reducing the period covered by this evaluation within which patients could commence treatment.

Our data identified fewer patients commenced on nintedanib for lung function deterioration compared to the INBUILD study.[4] A relative decline in FVC of >10% of predicted value was the most common criterion met to diagnose PF-ILD in the INBUILD treatment arm (160/332, 48.2%) compared to only 162/1120 (14.5%) in our study. Our study demonstrated a higher proportion of patients having progression defined by HRCT 418/1120 (37.3%) than those in the INBUILD treatment arm (62, 18.7%). FVC trajectories are known to be poorer in those with disease progression identified by HRCT and our data demonstrates real world practice of using HRCT to determine disease progression prior to treatment initiation.[11] This increased reliance on HRCT could reflect the reduced availability of lung function testing during the COVID-19 pandemic.[12] Regardless of the rationale, the increased use of HRCT to diagnose progression emphasises the requirement for specialist thoracic radiologist review in the context of an MDT. Accurate quantification of disease progression including the identification of subtle changes in disease extent and morphology may be aided by the use of artificial intelligence assessment of serial HRCT.[13]

PF-ILD encompasses a broad range of underlying ILD subtypes. This service evaluation highlights differences between our real-world patient cohort and that examined by the INBUILD study. A higher proportion of autoimmune ILDs (including RA-ILD and CTD-ILD) were seen in this service evaluation compared to the INBUILD nintedanib arm (377/1120 [33.7%] and 82/332 [24.7%] respectively), perhaps reflecting the exclusion of patients receiving concomitant immunosuppression in INBUILD.[4] Idiopathic NSIP and unclassifiable ILDs were under-represented in the real world study compared to INBUILD, 125/1120 (11.1%) vs 64/332 (19.3%) and 100/1120 (8.9%) vs 64/332 (19.3%) respectively. There were however significant similarities for example hypersensitivity pneumonitis was the most common underlying diagnosis in both the INBUILD nintedanib arm (84/332, 25.3%) and our service evaluation (298/1120, 26.7%).

These data have highlighted the use of nintedanib for PPFE (19/1120, 1.7%). Both PPFE and nintedanib use are associated with weight-loss and the adverse event rate of nintedanib in this population is unknown.[14,15] Evidence for the use of nintedanib in PPFE is limited to conflicting retrospective reports, highlighting the need for prospective, controlled studies.[16,17] Whilst the INBUILD study did include patients with PPFE they represented a small proportion of the overall cohort and were not analysed as a separate subgroup.[18] Patients being commenced on nintedanib for PPFE will require close monitoring and follow up to manage potentially burdensome adverse events.

Nintedanib has a broad range of anti-fibrotic, anti-inflammatory and vascular remodelling effects.[19] Immunosuppressive therapies have a myriad of mechanisms of action depending on the drug in question, different to those seen with nintedanib therapy. Combined immunosuppressive and anti-fibrotic may therefore offer synergistic effects of reducing the progression of ILD. Despite this promise there is limited trial or real-world data concerning the efficacy of co-prescription of these drugs[8]. Our data have highlighted the common use of nintedanib combined with immunosuppressive or modulatory therapies (Table 1). Oral corticosteroids (609/1120, 54.4%), MMF (335/1120, 29.9%), hydroxychloroquine (76/1120, 6.8%) and methotrexate (73/1120, 6.5%) were all commonly used alongside nintedanib.

The INBUILD Trial did not include participants taking concomitant immunosuppressive therapy, except for low dose corticosteroids, however 16% of participants were initiated on therapy other than nintedanib after 6 months.[4] In the treatment arm of the SENSCIS trial of nintedanib for systemic sclerosis, 48% (139/288) of patients were receiving MMF with a suggested beneficial effect of MMF on lung function decline and without increased adverse events when used in combination with nintedanib. However, the seminal PANTHER study of immunosuppression in IPF demonstrated the potential harmful effect of immunosuppression in patients with IPF. Consequently, the use of immunosuppression in the context of a progressive fibrosing phenotype with UIP pattern fibrosis requires further evidence to ensure greatest patient benefit and minimise potential harm.[20]

Within the SENSCIS trial adverse event rate in the nintedanib and placebo arms were similar between the subgroups receiving MMF and not.[7] The study reported 15/139 (10.8%) participants in the nintedanib group who were receiving MMF at baseline discontinued nintedanib treatment. By comparison we demonstrated an overall discontinuation rate for reasons other than death in 112/928 patients (12.1%). Limited real-world single centre tolerability data demonstrated no significant difference in nintedanib discontinuation rates, tolerability or side effect profile between cohorts receiving co-antifibrotic and immunosuppressive therapy and those receiving anti-fibrotic monotherapy.[21]

The overall discontinuation rate in our cohort (including death) was 175/928 (18.9%). Real-world UK data for the use of nintedanib in IPF demonstrate varying overall discontinuation rates ranging from 26% (32/119) to 30% (15/49).[22,23] The discrepancies between these data and those reported for our cohort may represent several factors including the shorter follow up period in our service evaluation, improvements in adverse effect management and differences in patient demographics and disease severity. It is encouraging that our real-world data suggests an acceptable tolerability profile of nintedanib in PF-ILD.

Importantly, 63/928 (6.8%) patients had the reason for nintedanib discontinuation recorded as death. The limitations of the data collected means we are unable to identify the duration of

treatment with nintedanib prior to death. The study does however identify a high proportion of patients commencing nintedanib with significant lung function impairment. 231/1120 (20.6%) had an FVC <50% at the time of MDT decision to commence nintedanib and 436/1120 (38.9%) had a DLCO <40%. This could reflect the recent approval of nintedanib for patients who previously had no anti-fibrotic treatment options and therefore had more advanced disease at the time of initiation. Whilst the unpredictable nature of ILD progression makes prognostication difficult, consideration of life expectancy and severity of lung function impairment should be considered prior to initiation of nintedanib to ensure the beneficial effect on lung function preservation remains greater than the symptom burden. In patients with high symptom burden and poor prognosis a supportive management approach may be more appropriate.

Limitations

There are several limitations to the reported service evaluation. Firstly, the service evaluation methodology was adopted to enable rapid data collection, as such the study did not record individual-level patient data. This limited the interpretation of individual patient prescribing patterns. The dose of oral corticosteroid and immunosuppression was also not recorded. The data did not capture patients who were, for example, prescribed oral corticosteroids and MMF with nintedanib. Furthermore, we are unable to elucidate whether those patients who discontinued nintedanib treatment were those on concomitant therapy or had greater impairment in lung function.

The NICE Guidance is only applicable to NHS England, Wales and Northern Ireland. Nintedanib has been available for PF-ILD prior to November 2021 in NHS Scotland. Our service evaluation may not have captured cohorts of patients commenced on nintedanib prior to this date. Furthermore patients were able to receive nintedanib on a named patient basis prior to November 2021 as reported by Raman *et al*.[8] These patients were purposely excluded from the current study but represent an important cohort of patients with PF-ILD who may benefit from nintedanib.

Despite these limitations, this study presents real-world data for the majority of UK prescribing centres and provides important practice-based evidence for the management of PF-ILD.

Conclusions

Nintedanib is widely prescribed in UK practice for the treatment of PF-ILD. Our service evaluation has demonstrated its use in a variety of underlying diagnoses, for a broad range of disease severity and commonly with concomitant immunosuppressive therapy. The service evaluation has highlighted variances in prescribing practices and important distinctions between real-world and clinical trial practice. Furthermore, we have emphasised gaps in the evidence base including the use of concomitant immunosuppression and anti-fibrotic therapy, the use of nintedanib in patients with severely impaired lung function and the increased use of HRCT to identify disease progression.

Acknowledgments

This work was undertaken during The Wellcome Trust GW4-CAT PhD Fellowship for GD and supported by the Research Capability Fund of the Royal United Hospitals Bath NHS Foundation Trust.

Drug	n	%
Oral corticosteroids	609	54.4%
Mycophenolate mofetil	355	31.7%
Hydroxychloroquine	76	6.8%
Methotrexate	73	6.5%
Rituximab	70	6.3%
Azathioprine	36	3.2%
Sulfasalazine	36	3.2%
Cyclophosphamide	13	1.2%
Abatacept	6	0.5%
Tacrolimus	6	0.5%
Leflunomide	5	0.4%
Tocilizumab	5	0.4%
Etanercept	3	0.3%
Other	11	1.0%

Table 1. Table demonstrating intended concomitant prescription of immunomodulatory or immunosuppressive therapy with nintedanib for progressive fibrosing interstitial lung disease 'Other' included Adalimumab, denosumab, baracitinib, IVIG, sildenafil, upadacitinib, certolizumab. Oral corticosteroids included any dose or preparation.

1. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev*. Dec 31 2018;27(150)doi:10.1183/16000617.0076-2018

2. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. *N Engl J Med*. Sep 3 2020;383(10):958-968. doi:10.1056/NEJMra2005230

3. Hambly N, Farooqi MM, Dvorkin-Gheva A, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. *Eur Respir J*. Oct 2022;60(4)doi:10.1183/13993003.02571-2021

4. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med*. 10 31 2019;381(18):1718-1727. doi:10.1056/NEJMoa1908681

5. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. May 29 2014;370(22):2071-82. doi:10.1056/NEJMoa1402584

6. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med*. Jun 27 2019;380(26):2518-2528. doi:10.1056/NEJMoa1903076

7. Highland KB, Distler O, Kuwana M, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med*. Jan 2021;9(1):96-106. doi:10.1016/S2213-2600(20)30330-1

8. Raman L, Stewart I, Barratt SL, et al. Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study. *ERJ Open Research*. 2022:00423-2022. doi:10.1183/23120541.00423-2022

9. NICE. Nintedanib for treating progressive fibrosing interstitial lung diseases. England2021.

10. Allen M. *Respiratory Medicine GIRFT Report*. 2021. *GIRFT Programme National Specialty Report*. https://gettingitrightfirsttime.co.uk/wp-content/uploads/2021/11/Respiratory-Medicine-Oct21L.pdf

11. Oldham JM, Lee CT, Wu Z, et al. Lung function trajectory in progressive fibrosing interstitial lung disease. *European Respiratory Journal*. 2022;59(6):2101396. doi:10.1183/13993003.01396-2021

12. McGowan A, Laveneziana P, Bayat S, et al. International consensus on lung function testing during the COVID-19 pandemic and beyond. *ERJ Open Res*. Jan 2022;8(1)doi:10.1183/23120541.00602-2021

13. Barnes H, Humphries SM, George PM, et al. Machine learning in radiology: the new frontier in interstitial lung diseases. *Lancet Digit Health*. Jan 2023;5(1):e41-e50. doi:10.1016/S2589-7500(22)00230-8

14. Kinoshita Y, Utsunomiya T, Koide Y, et al. Changes in body weight reflect disease progression in pleuroparenchymal fibroelastosis. *Respir Med Res*. Nov 26 2022;83:100980. doi:10.1016/j.resmer.2022.100980

15. Chen CH, Lin HC, Wang YH, Wang CY, Lin YS, Lai CC. The safety of nintedanib for the treatment of interstitial lung disease: A systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2021;16(5):e0251636. doi:10.1371/journal.pone.0251636

16. Nasser M, Si-Mohamed S, Turquier S, et al. Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis. *Orphanet J Rare Dis*. Oct 9 2021;16(1):419. doi:10.1186/s13023-021-02043-5

17. Kinoshita Y, Miyamura T, Ikeda T, et al. Limited efficacy of nintedanib for idiopathic pleuroparenchymal fibroelastosis. *Respir Investig*. Jul 2022;60(4):562-569. doi:10.1016/j.resinv.2022.03.001

18. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. May 2020;8(5):453-460. doi:10.1016/S2213-2600(20)30036-9

19. Wollin L, Distler JH, Denton CP, Gahlemann M. Rationale for the evaluation of nintedanib as a treatment for systemic sclerosis-associated interstitial lung disease. *J Scleroderma Relat Disord*. Oct 2019;4(3):212-218. doi:10.1177/2397198319841842

20. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. May 24 2012;366(21):1968-77. doi:10.1056/NEJMoa1113354

21. Newman K, Garfoot T, Stranks L, et al. P30 Real-world tolerability study of nintedanib in patients with progressive fibrosing interstitial lung disease compared to patients with idiopathic pulmonary fibrosis. *Thorax*. 2022;77(Suppl 1):A96-A96. doi:10.1136/thorax-2022-BTSabstracts.166

22. Barratt SL, Mulholland S, Al Jbour K, et al. South-West of England's Experience of the Safety and Tolerability Pirfenidone and Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis (IPF). *Front Pharmacol*. 2018;9:1480. doi:10.3389/fphar.2018.01480

23. Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis. *J Clin Med*. Sep 2 2016;5(9)doi:10.3390/jcm5090078

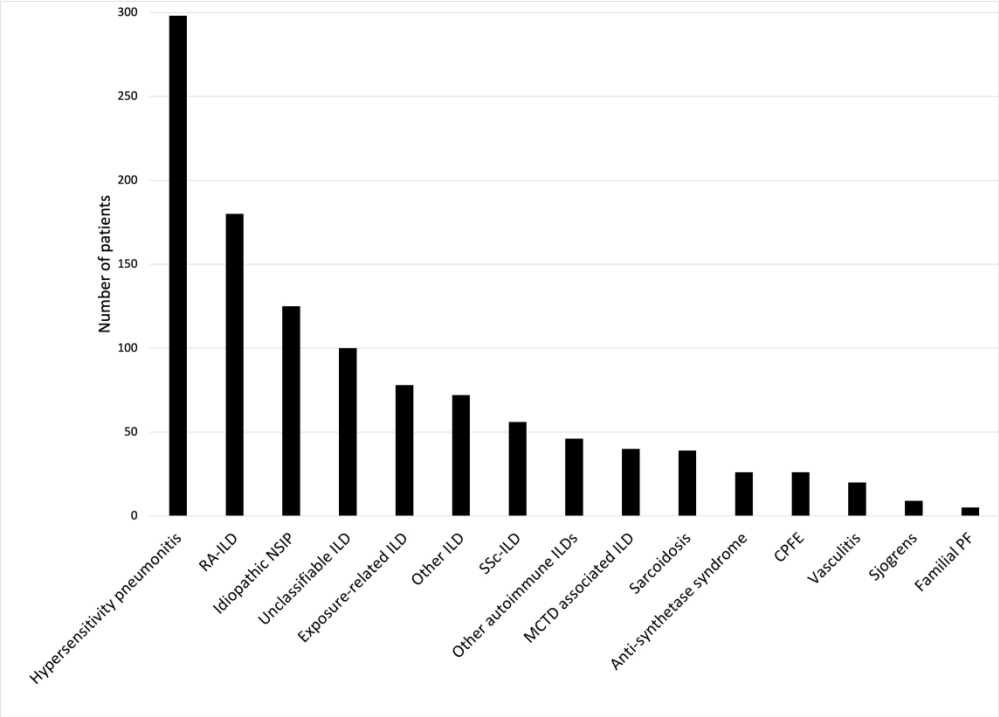
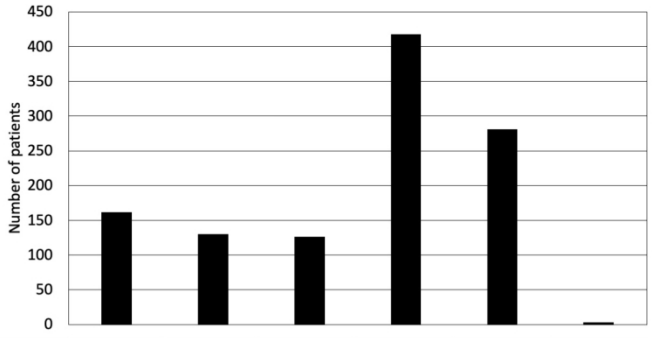


Figure 1. Primary diagnosis of 1120 patients with an ILD-MDT decision to commence nintedanib between 17th November 2021 and 30th September 2022. CPFE = Combined pulmonary fibrosis and emphysema syndrome, ILD = Interstitial lung disease, MCTD-ILD = Mixed connective tissue disease-ILD, NSIP =Non-specific interstitial pneumonia, PF = Pulmonary fibrosis, RA-ILD = Rheumatoid arthritis – ILD, SSc-ILD = Systemic sclerosis-ILD. The predominant diagnoses included in 'Other ILD' were pleuroparenchymal fibroelastosis (PPFE) 19/1120 (1.7%), other connective tissue disease-ILD 11/1120 (1.0%), fibrotic organising pneumonia 7/1120 (0.6%), interstitial pneumonia with autoimmune features 6/1120 (0.5%), asbestosis 5/1120 (0.4%), desquamative interstitial pneumonia 4/1120 (0.4%), post-Covid ILD 3/1120 (0.3%) and sarcoidosis 2/1120 (0.2%).

355x255mm (300 x 300 DPI)



Progression criteria	1	2	3	4	>1 criteria	Other
10% relative decline in FVC	+				+/-	
≥5% <10% decline in FVC		+	+		+/-	
Worsening respiratory symptoms		+		+	+/-	
Increasing fibrotic changes on HRCT			+	+	+/-	

Figure 2. Diagnostic criteria for progressive fibrosing interstitial lung disease in 1120 patients with an ILD-MDT decision to commence nintedanib between 17th November 2021 and 30th September 2022.

161x90mm (300 x 300 DPI)

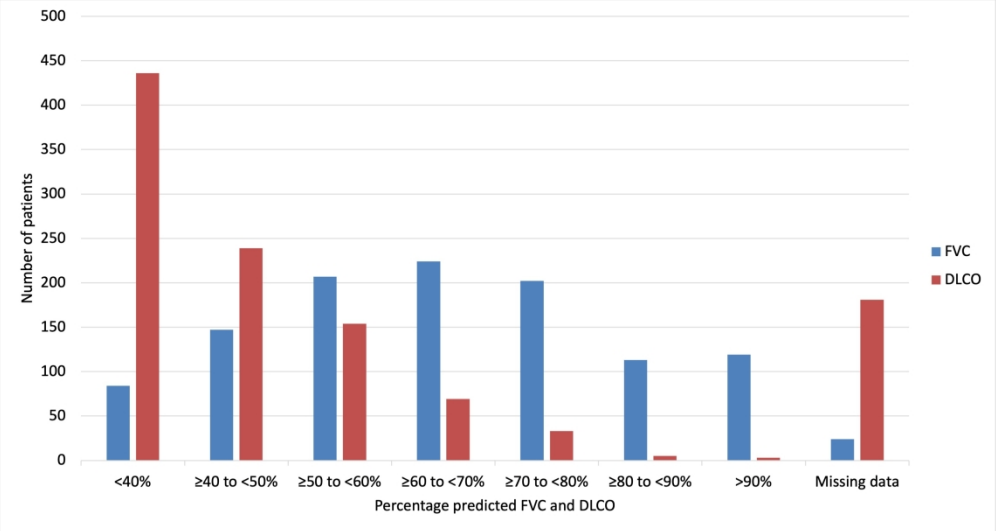


Figure 3. Percentage predicted forced vital capacity (FVC) and gas transfer (DLCO) for 1120 patients with an ILD-MDT decision to commence nintedanib between 17th November 2021 and 30th September 2022

282x151mm (300 x 300 DPI)

UK PF-ILD Nintedanib Service Evaluation

Page 1: A service evaluation of the UK Real-world use of nintedanib for PF-ILD.

Many thanks for offering to submit data for this national service evaluation of the use of nintedanib in progressive fibrosing ILD.

The Service Evaluation covers the time period of 17th November 2021 to 30th September 2022.

All contributors and supervisors will be included in the authorship of publications resulting from this work. All contributors and supervisors will be invited to review any proposed publication.

Please document names and centres as you wish them to be acknowledged in any future publications.

For any queries please contact gilesdixon@nhs.net

Basic information

1. Name of specialist ILD centre ✱ *Required*

2. Name of local service evaluation lead ✱ *Required*

3. Email address of service evaluation lead ✱ *Required*

Please enter a valid email address.

4. Name of supervising consultant (if applicable)

5. Email address of supervising consultant (if applicable)

Please enter a valid email address.

Diagnosis

6. How many patients have had an ILD MDT diagnosis of PF-ILD and have been prescribed (or are awaiting prescription) of nintedanib?

More info

Please enter a whole number (integer).

6.a. Of these patients which diagnostic criteria have been fulfilled to give diagnosis

More info

	Number of patients
A relative decline in FVC% predicted of at least 10% predicted in the past 24 months.	
A relative decline in FVC% predicted of at least 5% predicted, but less than 10% predicted with worsening respiratory symptoms	
A relative decline in FVC% predicted of at least 5% predicted, but less than 10% predicted with increasing fibrotic changes on HRCT compared in the past 24 months.	
Worsening respiratory symptoms and increasing fibrotic changes on high-resolution chest imaging in the past 24 months.	
≥1 diagnostic criteria	
Other diagnostic criteria (please state below with diagnosis and number of patients)	

6.a.i. If other please state diagnosis and number of patients. e.g. MDT consensus opinion of disease progression, x patients

6.b. Of these patients what has the **primary** diagnosis been

More info

	Number of patients
Hypersensitivity pneumonitis	
RA-ILD	
SSc-ILD	

Mixed connective tissue disease associated ILD	
Anti-synthetase syndrome	
Sjogrens	
Vasculitis	
Other autoimmune ILDs	
Idiopathic NSIP	
Unclassifiable idiopathic interstitial pneumonia	
Sarcoidosis	
Exposure-related ILD	
Familial PF	
CPFE	
Other ILD	

6.b.i. If other please state diagnosis and frequency e.g. x disease, x patients

Co-prescription

7. At the time of ILD MDT diagnosis of PF-ILD and decision to offer nintedanib, how many individual patients were taking the following medications for treatment of their ILD?

More info

	Number of patients taking medication at time of initiation of nintedanib
Abatacept	
Adalimumab	
Azathioprine	
Ciclosporin	
Denosumab	
Etanercept	
Hydroxychloroquine	
Infliximab	
Leflunomide	
Oral corticosteroids	
Methotrexate	
Mycophenolate mofetil	
Rituximab	
Sulfasalazine	
Tacrolimus	
Tocilizumab	
Other relevant for treatment of PF-ILD (see below)	

7.a. If other please state drug and number of patients. e.g. x drug, y patients

8. In how many patients have the following medications (for treatment of ILD) been stopped (or paused) in order to initiate nintedanib?

	Number of patients
Abatacept	
Adalimumab	
Azathioprine	
Ciclosporin	
Denosumab	
Etanercept	
Hydroxychloroquine	
Infliximab	
Leflunomide	
Oral corticosteroids	
Methotrexate	
Mycophenolate mofetil	
Rituximab	
Sulfasalazine	
Tacrolimus	
Tocilizumab	
Other relevant for treatment of PF-ILD (See below)	

8.a. If other please state drug and number of patients. e.g. x drug, y patients

Imaging

9. How many patients had the following predominant HRCT appearances

	Number of patients
Definite UIP	
Probable UIP	
Indeterminate UIP	
Fibrotic NSIP	
Fibrotic HP	
Alternative pattern	

Pulmonary Function Testing

10. How many patients had the following % predicted FVC range at the time of MDT decision to offer nintedanib for PF-ILD

	Number of patients
<40%	
≥40 to <50%	
≥50 to <60%	
≥60 to <70%	

≥70 to <80%	
≥80 to <90%	
≥90%	

11. How many patients had the following % predicted TLCO range at the time of MDT decision to offer nintedanib for PF-ILD

	Number of patients
<40%	
≥40 to <50%	
≥50 to <60%	
≥60 to <70%	
≥70 to <80%	
≥80 to <90%	
≥90%	

Drug initiation

12. As of 30th September 2022 how many patients have commenced nintedanib for PF-ILD?

More info

12.a. Of these patients how many have discontinued nintedanib?

12.b. What were the reasons for drug discontinuation?

	Number of patients
Death	
Drug tolerability	
Deranged LFTs	
Other	

12.b.i. If other please state reason and number of patients e.g. rash, x patients

Service delivery

13. Which services are initating nintedanib for PF-ILD? (Tick all that apply)

- ☐ ILD service
- ☐ Joint rheumatology/ILD service or equivalent
- ☐ Rheumatology service independent of ILD service
- ☐ General respiratory physician
- ☐ Other

13.a. If you selected Other, please specify:

14. Who are the prescribers of nintedanib for PF-ILD in your service? (Tick all that apply)

- [ ] Pharmacist
- [ ] Respiratory physician
- [ ] Rheumatologist
- [ ] Nurse specialist
- [ ] Specialist physiotherapist
- [ ] Other (please state)
- [ ] Other

14.a. If you selected Other, please specify:

Page 2: Final page

Many thanks for completing the service evaluation data collection form.

Your contribution is highly appreciated.

Giles, Michael and Shaney

Co-ordinating Centres

Bristol Interstitial Lung Disease Servive, North Bristol NHS Trust, Bristol, UK
Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK

Participating Centres

Antrim Area Hospital, Northern Health and Social Care Trust, Antrim, Northern Ireland, UK
Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK
Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
Hull University Teaching Hospitals NHS Trust, Hull, UK
Interstitial Lung Disease Unit, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK
Leeds Teaching Hospitals NHS Trust, Leeds, UK
Liverpool Interstitial Lung Disease Service, Aintree Hospital, Liverpool University Hospital NHS FT, Liverpool, UK
New Cross Hospital, The Royal Wolverhampton NHS Trust, Wolverhampton, UK
Norfolk and Norwich University Hospital NHS Foundation Trust, UK
Nottingham University Hospitals NHS Trust, Nottingham, UK
Oxford University Hospitals NHS Foundation Trust, Oxford, UK
Royal Brompton and Harefield Hospitals, London, UK
Royal Infirmary of Edinburgh, Edinburgh, UK
Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK
Southern Health and Social Care Trust, Northern Ireland, UK
St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK
University Hospital of Southampton NHS Foundation Trust, Southampton, UK
University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
University Hospitals of Morecambe Bay NHS Foundation Trust, Lancashire and South Cumbria ILD service, Lancaster, UK
University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

Centres listed in alphabetical order