A case of a patient with IPF treated with nintedanib

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Case Overview

This case describes the history of a patient with IPF who, at the time of diagnosis, had symptoms typical for IPF and a MSCT (multislice CT) consistent with Usual Interstitial Pneumonia (UIP). After 2 years without intervention his lung function declined and he was enrolled in the INPULSIS® trial (NCT01335464 and NCT01335477) and subsequently in the INPULSIS®-ON (NCT01619085) extension trial. Five years after diagnosis, the thin section multislice CT scan shows definite UIP and the patient continues on nintedanib.

www.clinicaltrials.gov
Medical history and tests

First presentation (2009)

Symptoms at first presentation (69-year-old male)

• Increasing dyspnoea on exertion for over 18 months
• 3 flights of stairs and sports (cycling and tennis) possible
• No angina pectoris
• Non-productive cough under exertion

Physical examination at first presentation

• 87 kg, 185 cm
• Bibasilar pulmonary velcro crackles
• Heart rate 54 beats/min
• No heart murmurs
• No leg oedema
Medical history and tests

Patient history
• No familial disposition for ILDs
• Office employee
• No allergies
• Ex-smoker (stopped 2 years ago, 40 pack years)
• No medication at first presentation

Pre-existing conditions
• Pneumonia 1 year ago
• Urethra surgery 15 years ago
• Mild hepatopathy of unknown aetiology
# Lung function

First presentation: Pulmonary function tests (2009)

<table>
<thead>
<tr>
<th>Value</th>
<th>2009</th>
<th>Absolute</th>
<th>% of predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.3</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.8</td>
<td>85</td>
<td></td>
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<tr>
<td>FEV₁ /FVC</td>
<td></td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.7</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.0</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>DL\textsubscript{CO}-SB</td>
<td></td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>DL\textsubscript{CO}/VA</td>
<td></td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Pa\textsubscript{O₂} at rest (mmHg)</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pa\textsubscript{CO₂} at rest (mmHg)</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Medical history and tests

First presentation: 6-minute walking test (2009)

• Distance walked: 520 m
• Initial $\text{SaO}_2$: 96%
• Minimal $\text{SaO}_2$: 91%
Laboratory

Laboratory results (2009)

Negative autoantibodies
- Anti-nuclear antibodies
- Extractable nuclear antigens, including JO-1, scl-70
- Rheumatoid factor
- Anti-CCP

Laboratory profile:
- Mildly elevated transaminases
- normal proBNP

Bronchoalveolar lavage (BAL)
- Regular cellular pattern
Imaging

Echocardiography (2009)

• Regular left ventricular function and normal diastolic function
• Regular right ventricular function (TAPSE: 20mm)
• Regular pulmonary artery systolic pressure (PASP)
• No pericardial effusion
• Mild sclerosis of the mitral and the aortic valves
Imaging- HRCT (2009)

Initial MSCT 2009
The initial MSCT (multislice CT) scan from 2009 shows

- Traction bronchiectasis
- Reticulation (basal and peripheral predominance)
- Ground glass opacity
- Minimal honeycombing

The pattern is consistent with Usual Interstitial Pneumonia (UIP), even though the extent of honeycombing is minimal.

In addition, the presence of relevant ground-glass opacifications may indicate acute inflammatory activity.

Imaging (1)

MSCT (2009)
Image description:
Initial MSCT 2009:
Ground glass opacities
Imaging (4)
Reticulation (2009)

Image description:
Initial MSCT 2009: Reticulation
Imaging (6)
Minimal honeycombing (2009)

Image description:
Initial MSCT 2009:
Minimal honeycombing
Image description:
Initial MSCT 2009:
Traction bronchiectasis
Image description:
Initial MSCT 2009:
Disease distribution (sagittal reformat: „lateral view“)

sagittal reformat „lateral view“
Question 1
Which answers are correct?
1. „A“ shows traction bronchiectasis
2. „A“ shows honeycombing*
3. „B“ shows traction bronchiectasis*
4. „B“ shows honeycombing
Answer 1
2 + 3
A = honeycombing
B = traction bronchiectasis
Diagnosis

In a patient whose HRCT or MSCT shows a UIP pattern, the following main differential diagnoses have to be considered:

• Idiopathic pulmonary fibrosis (IPF)
• Connective tissue disease associated interstitial lung disease (CTD-ILD)
• Asbestosis
• Drug induced interstitial lung disease
• Chronic hypersensitivity pneumonitis
• Familial interstitial pneumonias
• Rare etiologies, e.g. Hermansky-Pudlak syndrome

The patient’s history, clinical and radiological findings were discussed initially in our multidisciplinary ILD Board discussion and the diagnosis of Idiopathic Pulmonary Fibrosis (IPF) was made.

Question 2

Which of the following is **not** true?

1. IPF diagnosis relies on clinical, radiological and, where necessary, pathological criteria to be discussed in a multidisciplinary team
2. For the diagnosis of IPF a contrast enhanced CT scan is mandatory *
3. Clinical information in diagnosis should focus on the exclusion of secondary causes, such as drug induced ILD, chronic hypersensitivity pneumonitis or connective tissue disease associated ILD
4. A patient with possible UIP pattern on HRCT or MSCT should undergo surgical lung biopsy if possible
This is not true: For the diagnosis of IPF a contrast enhanced CT scan is mandatory.

As stated in the combined 2011 ATS/ERS/JRS/ALAT guidelines,

- IPF diagnosis relies on clinical, radiological and, where necessary, pathological criteria to be discussed in a multidisciplinary team
- Clinical information in diagnosis should focus on the exclusion of secondary causes, such as drug induced ILD, chronic hypersensitivity pneumonitis or connective tissue disease associated ILD
- A patient with possible UIP pattern on HRCT/MSCT should undergo surgical lung biopsy if possible

A contrast enhanced CT, on the other hand, is not suitable for the detection of HRCT patterns of the lung.
Outpatient clinic

Recommended therapies (2009)

The following therapies were recommended in 2009:

• Ambulatory rehabilitation (“lung sports”)

• Vaccination against pneumococci and influenza

• Different therapeutic options at that time (N-acetyl cysteine, immunosuppression, clinical trial, wait and watch) were thoroughly discussed.*

The patient’s preference included a clinical trial for which he was not eligible due to elevated transaminase levels and alternatively he then chose a wait and watch strategy.

*Since then, several new trials and updated treatment guidelines (Raghu G, et al. AJRCCM 2015;192:e3–e19) have been published.
Lung function

Lung function 2 years after diagnosis (2012)

2 years after diagnosis, a 300 ml decrease in the FVC (8% absolute change) and an absolute 5% decrease in DL$_{CO}$ were noted.
### Lung function (2)

#### Lung function tests at initiation of INPULSIS® (2012)

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<th>2009 Absolute</th>
<th>% of predicted</th>
<th>2012 Absolute</th>
<th>% of predicted</th>
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<tr>
<td>FVC (L)</td>
<td>3.3</td>
<td>73</td>
<td>2.95 l</td>
<td>67</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
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<td>85</td>
<td>2.55 l</td>
<td>75</td>
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<tr>
<td>FEV₁ % VC MAX (%)</td>
<td>85 %</td>
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<td></td>
<td></td>
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<tr>
<td>RV (L)</td>
<td>1.7</td>
<td>66</td>
<td>1.5 l</td>
<td>54</td>
</tr>
<tr>
<td>TLC (L)</td>
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<td>4.5 l</td>
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<tr>
<td>RV % TLC (%)</td>
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<td></td>
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<td>DL\textsubscript{CO}-SB</td>
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<td>61%</td>
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<td>(\text{Pa}_\text{O}_2) at rest (mmHg)</td>
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<td>78</td>
<td></td>
<td></td>
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<tr>
<td>(\text{Pa}_\text{CO}_2) at rest (mmHg)</td>
<td>41</td>
<td>39</td>
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</table>
PFT at initiation of INPULSIS® trial (nintedanib vs placebo; double-blinded)
Outpatient Clinic (2012)

MDT discussion in 2012
Following further discussions at the multidisciplinary ILD board on the different therapeutic options available at the time (now including pirfenidone or inclusion in the INPULSIS® trial), the patient opted for the INPULSIS® trial.

INPULSIS® study design
• 3:2 randomisation ratio for nintedanib:placebo
• Dose interruption and/or dose reduction to 100 mg twice daily allowed to manage adverse events
• Patients who prematurely discontinued trial drug were asked to attend all visits as planned

Outpatient clinic (2012)
INPULSIS® study design

Outpatient clinic

Continuation with INPULSIS®-ON (2012)

After one year in INPULSIS® trial, the patient continued with INPULSIS®-ON (open label extension trial with nintedanib; NCT01619085)

www.clinicaltrials.gov
Crestani B, Oral presentation, Session 462, ERS 2015
Outpatient clinic
Continuation with INPULSIS®-ON (2)

Patients randomized 3:2
To receive either nintedanib or placebo

INPULSIS®
Nintedanib 150 mg bid
Placebo

52 Weeks (trial period)

INPULSIS®-ON
Continuing nintedanib
Initiating nintedanib

~4 Week Follow-up (no treatment)
Extension trial (open-label treatment with nintedanib)

www.clinicaltrials.gov
Crestani B, Oral presentation, Session 462, ERS 2015
Lung function tests after open label treatment with nintedanib (2014 and 2016)

<table>
<thead>
<tr>
<th>Value</th>
<th>2014 (1 year)</th>
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<td>Absolute</td>
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<td>TLC (L)</td>
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<td>RV % TLC (%)</td>
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<tr>
<td>DLco-SB</td>
<td>55%</td>
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<tr>
<td>PaO₂ at rest (mmHg)</td>
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<tr>
<td>PaCO₂ at rest (mmHg)</td>
<td>30 mmHg</td>
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Outpatient clinic

Side effect management

• During his participation in the double-blinded INPULSIS® trial and its open-label extension trial INPULSIS®-ON, the patient noticed some diarrhea.

• This disappeared with intermittent dose reductions and was manageable with intermittent use of loperamide.
Ward

Pneumonia (1/2013)

• The patient required hospitalization for pneumonia
• After antibiotic treatment, his general condition improved rapidly
• Significant decrease in lung function was not noted
Imaging (1) (2014)

MSCT features 5 years later (2014)
Imaging

MSCT 5 years after diagnosis (2014)

MSCT scan taken after 1 year in INPULSIS® trial (nintedanib vs placebo; double-blinded) and 1 year with nintedanib in the open-label extension trial INPULSIS®-ON (5 years after the first MSCT scan):

Typical signs of a long-term disease course in an IPF survivor:

• Definite **UIP** pattern

• Ground glass opacifications developed into **reticular** patterns

• Reticulation developed into **honeycombing** (irreversible end stage)

Initial HRCT (left) shows reticulation.

5 years later (right) reticulation (yellow) has increased and has partly developed into honeycombing (turquoise).
Initial HRCT (left) shows reticulation.

5 years later (right) reticulation (yellow) has increased and has partly developed into honeycombing (turquoise).
Initial HRCT (left) shows ground glass opacities.

5 years later (right) ground glass opacities (yellow) have increased and have partly developed into reticulation (turquoise).
Initial HRCT (left) shows ground glass opacities.

5 years later (right) the area of ground glass opacity has developed into reticulation (turquoise) and a new area of ground glass opacities (yellow) has developed.
Initial HRCT (left) shows traction bronchiectasis.

5 years later (right) traction bronchiectasis has increased.
Initial HRCT (left) shows traction bronchiectasis.

5 years later (right) traction bronchiectasis has increased.
Initial HRCT (left) shows minimal honeycombing.

5 years later (right) definite honeycombing can be seen.
Initial HRCT (left) shows minimal honeycombing.

5 years later (right) definite honeycombing can be seen.
Imaging

MSCT 7 years after diagnosis (2016)

Typical signs of a long-term disease course in an IPF survivor:

• Definite UIP pattern

• Ground glass opacifications developed into reticular patterns

• Reticulation developed into honeycombing (irreversible end stage)

tract. bronch. reticulation

↑tract. bronch. honeycombing ↑reticulation

↑tract. bronch. honeycombing ↑reticulation
Question 2
What can be seen in the marked areas?

1. Honeycombing
2. Reticulation
3. Traction bronchiectasis
4. Ground glass opacification
Reticulation
Question 3
What can be seen in the marked area?

1. Honeycombing
2. Reticulation
3. Traction bronchiectasis
4. Ground glass opacification
Answer 3

3

Traction bronchiectasis
Question 4

What can be seen in the marked area?

1. Honeycombing
2. Reticulation
3. Traction bronchiectasis
4. Ground glass opacification
Ground glass opacification
Learnings from the case
Take-home messages

1. **MDT** discussion is necessary for a correct diagnosis of IPF

2. Successful **management** of nintedanib **side effects** (eg, diarrhea) is possible and can help patients to stay on treatment

3. In this case, treatment with nintedanib is the most probable explanation of the positive long term course with **slow disease progression** (moderate decline of lung function parameters and long term stability on HRCT)

4. In this case, treatment with nintedanib might have **prevented exacerbations**