Case 12

IPF treatment with nintedanib

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Case Overview

Two medications are approved in the US and the EU for the treatment of idiopathic pulmonary fibrosis (as of July 2015).

This case shows an example of how patients that are treated with nintedanib and experience side effects (in this case, diarrhoea) can continue treatment and be effectively managed with lifestyle modification, dose reduction and the introduction of anti-diarrhoeal medication.
Medical History and Tests

- 69 year old man
- 12 months progressive exertional dyspnoea
- Well preserved exercise tolerance
- Ischaemic heart disease

Current medication:
- Rx – ASA, statin, β blocker

Physical Examination:
- No clubbing
- Bibasal crepitations
Laboratory

- Normal full blood count, urea and electrolytes and liver function tests
- ESR 12, CRP 3
- Negative autoimmune profile
- Negative serum precipitins
Imaging

Chest X-ray

- Minor loss of lung volume
- Haziness of diaphragms (arrow)
- Reticular change in lower zones bilaterally
Imaging

Minor loss of lung volume, haziness of diaphragms (arrow), reticular change in lower zones bilaterally
Imaging

CT Scan

• Coarse, sub-pleural reticulation verging on honeycomb destruction (circle)
• Traction bronchiectasis (arrow)
• Minor para-septal emphysema
Coarse, sub-pleural reticulation verging on honeycomb destruction (circle), traction bronchiectasis (arrow), minor para-septal emphysema
Question 1

What is the diagnosis?

1. Definite IPF*
2. Possible IPF
3. Hypersensitivity pneumonitis
4. Sarcoidosis

Correct answer: 1. Definite IPF
Answer 1

Author’s Solution:
Multidisciplinary Team (MDT) diagnosis = definite IPF
Diagnosis

- Classical CT appearance of UIP
- Absence of any alternative cause
- Appropriate clinical history for IPF

MDT diagnosis = definite IPF
Lung function

<table>
<thead>
<tr>
<th>Value</th>
<th>Absolute</th>
<th>% Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>3.50</td>
<td>108.8</td>
</tr>
<tr>
<td>FVC</td>
<td>3.97</td>
<td>95.2</td>
</tr>
<tr>
<td>VC MAX</td>
<td>4.04</td>
<td>93.3</td>
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<tr>
<td>TLCO-SB</td>
<td>4.46</td>
<td>47.9</td>
</tr>
<tr>
<td>TLCOc</td>
<td>4.44</td>
<td>47.6</td>
</tr>
<tr>
<td>VA</td>
<td>4.87</td>
<td>74.9</td>
</tr>
<tr>
<td>KCO</td>
<td>0.92</td>
<td>69.0</td>
</tr>
<tr>
<td>KCOc</td>
<td>0.91</td>
<td>68.6</td>
</tr>
<tr>
<td>TLC</td>
<td>5.46</td>
<td>76.4</td>
</tr>
<tr>
<td>RV</td>
<td>1.41</td>
<td>54.8</td>
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</table>

Date: 09/2010
- Well preserved dynamic lung volumes (FVC)
- But reduced static lung volume (TLC)
- With impairment of gas exchange (TLco)
Question 2

How would you treat this patient? (multiple answers possible)

1. Pirfenidone*
2. Nintedanib*
3. NAC
4. Prednisolone
5. Observation
6. Clinical Trial*

Correct Answer: 1, 2 and 6
Answer 2

Author’s Solution

Patient entered into clinical trial (INPULSIS®) as no active therapies were available at the time.

If being seen today I would commence anti-fibrotic therapy

- Patient has established disease on CT scan with evidence of functional impairment (Preservation of FVC is likely secondary to element of para-septal emphysema)
Outpatient clinic

Patient entered into clinical trial (INPULSIS®) in September 2011.

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

Nintedanib 150 mg

Screening

Visit 1

Placebo

Follow-up

Week

0 2 4 6 12 18 24 30 36 44 52 56

R
Medical History and Tests

- Tolerated “treatment” well with no side effects
- Mild progression in breathlessness
- FVC declined from 3.97 l to 3.52 l over 12 months
- Option to go into open label roll-over study
- October 2012 - started nintedanib 150 mg twice daily
Outpatient clinic

January 2013

• Well and asymptomatic for first 3 months on treatment
• 1kg weight loss (starting weight 72 kg)
• Reports wife had “stomach upset”
• A week later he developed diarrhoea – loose motions 2 – 3 times per day with urgency
• Reported symptoms after 10 days
• Clinically, well hydrated, normal abdominal examination
Question 3

How would you manage this patient?

1. Permanently discontinue nintedanib
2. Continue nintedanib 150 mg twice daily but commence loperamide*
3. Reduce nintedanib to 100 mg twice daily
4. Temporarily discontinue nintedanib and commence loperamide
5. Refer to gastroenterologist

Correct answer: 2
Answer 3

Author’s Solution

Continue nintedanib 150 mg twice daily but commence loperamide (also see "Management of Diarrhoea" table on next slide)
Outpatient clinic

- Started loperamide (also see „Management of Diarrhoea“ table)
- Improvement in diarrhoea
- However, 8 weeks later, further recurrence of diarrhoea
- Bowels open 4 – 5 times per day
- Unable to leave house because of urgency
- Weight reduced from 72 Kg to 67 Kg
## Outpatient clinic

### Management of Diarrhoea

<table>
<thead>
<tr>
<th>Description</th>
<th>Action for nintedanib</th>
<th>Symptomatic treatment</th>
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<tbody>
<tr>
<td><strong>Mild diarrhoea:</strong></td>
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<td>&lt;4 stools per day over baseline</td>
<td>Continue same nintedanib dose</td>
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<td>4–6 stools per day over baseline</td>
<td>If diarrhoea persists for ≥48-72 hours: 1. Interrupt nintedanib 2. Reduce dose to 100 mg BID 3. Re-escalate to 150 mg BID if appropriate</td>
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<td>Consider stool work-up; aggressive IV fluid replacement ≥24 hrs; hospitalisation; referral to a GI specialist</td>
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Question 4

How would you manage this patient?

1. Permanently discontinue nintedanib
2. Continue nintedanib 150 mg twice daily but commence loperamide
3. Reduce nintedanib to 100 mg twice daily
4. Temporarily discontinue nintedanib and commence loperamide*
5. Refer to gastroenterologist

Correct answer: 4.
Answer 4

Author’s Solution

Temporarily discontinue nintedanib and commence loperamide
Outpatient clinic

- Four week dose interruption
- Diarrhoea improved but still opening bowels twice per day
- Weight stabilised
- Recommenced 150 mg twice daily
- 4 weeks later, return of diarrhoea with further 2kg weight loss
## Management of Diarrhoea

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Question 5

How would you manage this patient?

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2. Continue nintedanib 150 mg twice daily but commence loperamide
3. Reduce nintedanib to 100 mg twice daily
4. Temporarily discontinue nintedanib and commence loperamide
5. Refer to gastroenterologist*

Correct answer: 5.
Answer 5

Author’s Solution

Refer to gastroenterologist
Medical History and Tests

• Seen by gastroenterologist
• Normal colonoscopy
• Started on codeine phosphate + loperamide
• Down titrated nintedanib to 100 mg twice daily
• 12 months later – tolerating therapy
• Opens bowels “more than I used to in the past” but is willing to tolerate this to be on treatment
• Dyspnoea stable
• FVC 3.42 (was 3.52 l in October 2012)
• Weight remains 67Kg
## Medical History and Tests

### Management of Diarrhoea

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Learnings From The Case

The most important take home messages of the case are:

1. Treatment is important to patients
2. Nintedanib can cause intrusive diarrhoea
3. As in this case diarrhoea can frequently be managed with lifestyle modification, dose reduction and the introduction of anti diarrhoeal medication