Data to Evidence: OHDSI in Action!

Rebecca Chandler, MD
Uppsala Monitoring Centre

Patrick Ryan, PhD
Janssen Research and Development
Columbia University Medical Center
The origins of pharmacovigilance

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (‘Distaval’) during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.
W. G. McBride.

* * * In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide (‘Distaval’) with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—Eb.L.
Scientists find a new clue about how thalidomide caused devastating birth defects

By MEGAN THIELKING @megaphone / AUGUST 3, 2018
WHO Programme for International Drug Monitoring

Thalidomide 1961

In 1968 WHO creates the Programme for International Drug Monitoring

In 1978 Swedish Government and WHO creates UMC and Collaborating Centre
Uppsala Monitoring Centre (UMC)  
WHO Collaborating Centre for International Drug Monitoring

- Established as a foundation in 1978
- Provider of scientific leadership and operational support to the WHO PIDM
- Custodian and manager of VigiBase®
- Maintenance organization for WHODrug™
- Self funding
UMC's Vision

Our vision is a world where all patients and health professionals make wise therapeutic decisions in their use of medicines.
How patient experiences are transformed to data

WHO Drug

MedDRA

VigiBase

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01011011011
11111100010
10100111011
Covering 90% of the world

UMC has developed and maintained VigiBase, the WHO global database of individual case safety reports (ICSRs), since 1978. Following the ten founder members of the late 60s, over 130 countries have now joined the WHO Programme, in all representing over 90% of the world’s population.

Total reports, as of 25 March 2019:

18 800 662

The WHO Programme for International Drug Monitoring
The basis of signal detection in pharmacovigilance

Fig. 1: Shrinkage of CI of IC over time
With increasing data, the confidence interval gets smaller. Once the value 0 is not included in the CI, a signal is flagged.

(Sten Olsson, the Uppsala Monitoring Centre, presentation, 2004)
UMC Signal detection process

1. National PV centres
2. VigiBase
3. First-pass statistical screening → Initial manual assessment
4. "Sprint"
5. In-depth manual assessment → Signal

Additional texts:
- "Sprint"
- Drug Safety
- PDS (Pharmacovigilance & Drug Safety)
- VigiBase
- National PV centres
- Initial manual assessment
Sprint Interface

Welcome Rebecca!
Welcome to the sprint interface.

Sprint progress

- **3** Combinations assigned
- **2** Combinations finalized
- **1** Potential signals

Potential signals

<table>
<thead>
<tr>
<th>Association Id</th>
<th>Drug</th>
<th>ADR</th>
<th>Assessor</th>
<th>Medic</th>
<th>Finalized date</th>
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<tbody>
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<td>419860</td>
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<td>Tumour lysis syndrome</td>
<td>RC</td>
<td>RC</td>
<td>2010-03-27</td>
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</table>

Your progress

- **3** Combinations assigned
- **2** Combinations finalized

Refresh start page
Sprint Interface

<table>
<thead>
<tr>
<th>Drug</th>
<th>Association</th>
<th>Excess 95% CI</th>
<th>Excess 95% CI</th>
<th>p-value</th>
<th>Yes or No</th>
<th>% Serious</th>
<th>Fatal</th>
<th>HLIT</th>
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<tbody>
<tr>
<td>Pneumococcal vaccine/hepatitis B vaccine</td>
<td>0.24</td>
<td>4.0</td>
<td>4.2</td>
<td>0.1</td>
<td>Yes</td>
<td>100</td>
<td>0</td>
<td>Haemophilus infections/avascular bacterial infections</td>
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<td>Carboplatin</td>
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<td>5.2</td>
<td>4.5</td>
<td>0.0</td>
<td>Yes</td>
<td>54</td>
<td>5</td>
<td>Electroyte imbalance, necrosis and vascular insufficiency</td>
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<td>Olopatadine</td>
<td>0.24</td>
<td>6.2</td>
<td>4.5</td>
<td>0.0</td>
<td>Yes</td>
<td>75</td>
<td>0</td>
<td>Endocrine autoimmune disorders/hypothyroidism disorders</td>
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<td>Sancalumab</td>
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<td>5.2</td>
<td>4.5</td>
<td>0.0</td>
<td>Yes</td>
<td>100</td>
<td>0</td>
<td>Heart failure, NEC/renal failure and impairment</td>
</tr>
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</table>

Showing 1 to 5 of 100 entries
Sprint Interface

### Sacubitril valsartan sodium hydrate - Cardiorenal syndrome

#### Assessor comments

![Assessor comments field]

#### Information

<table>
<thead>
<tr>
<th>Combination metrics</th>
<th>Report metrics</th>
<th>vigiRank metrics</th>
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<td><strong>Serious</strong></td>
<td><strong>Observed</strong></td>
<td><strong>vigiRank</strong></td>
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<td>1</td>
<td>20</td>
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<td><strong>IC</strong></td>
<td><strong>Expected</strong></td>
<td><strong>Informative</strong></td>
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<td>5</td>
<td>0.10</td>
<td>6</td>
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<tr>
<td><strong>IC825</strong></td>
<td><strong>Fatal cases</strong></td>
<td><strong>Narrative count</strong></td>
</tr>
<tr>
<td>4.3</td>
<td>7</td>
<td>10</td>
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<tr>
<td><strong>Drug report count</strong></td>
<td><strong>Serious proportion (%)</strong></td>
<td><strong>Recent reports</strong></td>
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<td>23555</td>
<td>100</td>
<td>20</td>
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<tr>
<td><strong>ADR report count</strong></td>
<td><strong>Total number of countries</strong></td>
<td><strong>Countries with IC&gt;0</strong></td>
</tr>
<tr>
<td>118</td>
<td>7</td>
<td>7</td>
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<tr>
<td><strong>First report</strong></td>
<td><strong>Dechallenge</strong></td>
<td><strong>IC Grand</strong></td>
</tr>
<tr>
<td>2016-07-11</td>
<td>0</td>
<td>1</td>
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<tr>
<td><strong>Last report</strong></td>
<td><strong>Rechallenge</strong></td>
<td><strong>IC Grand reason</strong></td>
</tr>
<tr>
<td>2018-10-27</td>
<td>0</td>
<td>IC825 &gt; 0</td>
</tr>
<tr>
<td><strong>First report for drug</strong></td>
<td><strong>Severity count</strong></td>
<td></td>
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<tr>
<td>2011-10-63</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td><strong>Narrative proportion (%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Study Report proportion (%)</strong></td>
<td></td>
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<td>35</td>
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<td></td>
<td><strong>Single suspected</strong></td>
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<tr>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Single suspected proportion (%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>
5.3 Gastrointestinal Disorders

Diarrhea

Diarrhea was the most frequent gastrointestinal event reported in 62\% versus 18\% of patients treated with OFEV and placebo, respectively [see Adverse Reactions (6.1)]. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11\% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5\% of the patients compared to less than 1\% of placebo-treated patients.

5.7 Gastrointestinal Perforation

Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3\% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs.
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Lucia Righi, M.D., Ph.D., Federico di Renzo, M.D., Davide Ruggeri, M.D., Anna Faccio, M.D., Massimo Talamini, M.D., and Trudy G. Kesten, M.D.*

*Corresponding author. E-mail: tkesten@ucsf.edu

The New England Journal of Medicine
May 20, 2016
Volume 374, Issue 20

ABSTRACT

Nintedanib (formerly known as BIBR 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that maintenance with 150 mg of nintedanib twice daily reduced lung-function decline and exacerbations in patients with idiopathic pulmonary fibrosis.

Methods

We conducted two phase 2 trials, randomized, double-blind, phase 2 triple-blind (INPULSiO-1 and INPULSiO-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary endpoint was the annual rate of decline in forced vital capacity (FVC). Key secondary endpoints were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

Results

A total of 1,069 patients were randomly assigned in a 1:1 ratio to receive nintedanib or placebo. The annual rate of change in FVC was -14.7 mL with nintedanib versus -20.6 mL with placebo (difference, 5.8 mL; 95% confidence interval, 5.7 to 12.4; P<0.001) in INPULSiO-1 and -15.5 mL with nintedanib versus -20.7 mL with placebo (difference, 5.2 mL; 95% CI, 4.4 to 6.0; P<0.001) in INPULSiO-2. In INPULSiO-1, there was a significant difference between the standard and placebo groups in the time to the first acute exacerbation (hazard ratio with standard, 1.1% CI, 0.55 to 2.6; P=0.4). In INPULSiO-2, there was a significant benefit with nintedanib versus placebo (hazard ratio: 0.88; 95% CI, 0.75 to 0.97; P=0.02). The most frequent adverse event in the standard groups was diarrhea, with rates of 23.7% and 19.3% in the standard and placebo groups, respectively, in INPULSiO-1 and 43.2% and 39.4% in the two groups, respectively, in INPULSiO-2.

Efficacy

In patients with idiopathic pulmonary fibrosis, nintedanib slowed the decline in FVC, which is consistent with a slowing of disease progression. Standard was frequently associated with diarrhea, which led us to discontinue the study medication in more than 1% of patients. (Funded by Bristol-Myers Squibb and Iyushen.)

In BIBR 1120, the clinical benefits of nintedanib were also achieved in patients with idiopathic pulmonary fibrosis.
Nintedanib

Adverse Event Management

This section is dedicated to the improvement of possible gastrointestinal side effects of OFEV®.

Treat diarrhea at the first sign

Diarrhea should be treated at first signs with adequate hydration and antidiarrheal medicinal products (e.g., loperamide), and may require treatment interruption or reduction of dose.¹

OFEV®: management of diarrhea

<table>
<thead>
<tr>
<th>1. Supportive medications</th>
<th>2. Dose adjustment</th>
<th>3. Dietary changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initiate antidiarrheals, such as loperamide</td>
<td>• Interruption or reduction of dose of OFEV® (nintedanib) should be considered if symptomatic treatment is ineffective</td>
<td>• Adequate hydration</td>
</tr>
<tr>
<td></td>
<td>• If diarrhea persists despite symptomatic treatment, therapy with OFEV® should be discontinued</td>
<td>• Avoidance of certain foods/drinks</td>
</tr>
</tbody>
</table>

https://www.inoncology.com/compounds/nintedanib/about
Ischaemic colitis

• A condition which arises with acute, transient compromise in blood flow to the mucosa of the colon

• Leads to mucosal ulceration, inflammation, and haemorrhage.

• It can be difficult to differentiate from other forms, such as infectious or inflammatory colitis

• High mortality rate
Ischaemic colitis

- Acute onset of abdominal pain, colicky in nature, diarrhoea and rectal bleeding
- Causes can be physiological or iatrogenic
- Should be recognised by generalists as colonoscopy recommended within 48 hours of onset of symptoms
- Surgical or conservative treatment
A question of causality

Bradford Hill Criteria

Temporality

Analogy

Plausibility

Consistency

Strength of Association

Dose-Response Relationship

Specificity

Experiment

Coherence

Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia
A Model for Assessing Causal Association in Pharmacovigilance

Michael Perrio, Simon Voss and Saad AW Shakir

1 Drug Safety Research Unit, Bursledon Hall, Southampton, UK
2 Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, UK
3 University of Portsmouth, Portsmouth, UK
A survey of 18 organs of normal adult mice revealed significant regression of capillaries in some organs and not in others (Kamba et al., 2006; Baffert et al., 2006a). After inhibition of VEGF signalling for 1 to 3 weeks, significant capillary regression occurred in pancreatic islets (Figure 2A and B), thyroid, adrenal cortex, pituitary, villi of small intestine (Figure 2C and D), choroid plexus, adipose tissue, and trachea (Kamba et al., 2006; Baffert et al., 2006a). The amount of regression was dose-dependent and varied from organ to organ, with a maximum of 68% in thyroid. But two tumours examined under the same conditions had even greater vascular regression (Inai et al., 2004; Kamba et al., 2006). Little or no capillary regression was detected in brain, retina, skeletal muscle, cardiac muscle, or lung under these conditions. Capillaries that underwent regression had the same pericyte coverage and apparent structural maturity as capillaries that survived.
Strength of association

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reaction (PT)</th>
<th>N_{observed}</th>
<th>N_{expected}</th>
<th>K_{cs}</th>
<th>IC</th>
<th>N_{survey}</th>
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</thead>
<tbody>
<tr>
<td>Nirtedanib</td>
<td>Large intestine perforation</td>
<td>11</td>
<td>1.47</td>
<td>1.57</td>
<td>2.55</td>
<td>7</td>
</tr>
<tr>
<td>Nirtedanib</td>
<td>Cecitis ischemic</td>
<td>6</td>
<td>1.44</td>
<td>0.37</td>
<td>1.75</td>
<td>3</td>
</tr>
<tr>
<td>Nirtedanib</td>
<td>Large intestinal hemorrhage</td>
<td>3</td>
<td>0.51</td>
<td>-0.26</td>
<td>1.79</td>
<td>2</td>
</tr>
<tr>
<td>Nirtedanib</td>
<td>Intestinal ischemia</td>
<td>3</td>
<td>1.00</td>
<td>-0.83</td>
<td>1.22</td>
<td>2</td>
</tr>
<tr>
<td>Nirtedanib</td>
<td>Gastrointestinal necrosis</td>
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<td>0.02</td>
<td>-1.43</td>
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<td>2</td>
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<tr>
<td>Nirtedanib</td>
<td>Intramural infarction</td>
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<td>0.19</td>
<td>-2.69</td>
<td>1.11</td>
<td>1</td>
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</table>
Analogy

SHORT REPORT

Ischaemic colitis associated with intravitreal administration of aflibercept: A first case report

Benjamin Botteux, Valérie Gras, Yanis Mahboud, Sophie Liabeuf, Youssef Bennis, Kamel Masmoudi

First published: 04 January 2019  |  https://doi.org/10.1111/bcp.13853

Abstract

In patients with age-related macular degeneration (AMD), the intravitreal injection of antivascular endothelial growth factor (anti-VEGF) agents reduces disease progression and choroidal neovascularization. We report on a first case of ischaemic colitis associated with intravitreal injection of the anti-VEGF agent aflibercept in an 80-year-old female patient. Conservative treatment resulted in a favourable clinical outcome. The anti-VEGF agent was discontinued, and the symptoms did not recur. Although the intravitreal injection of anti-VEGF agents has not previously been linked to the occurrence of ischaemic colitis, consideration of aflibercept’s pharmacological properties and the chronological relationship between the administration of this anti-VEGF agent and the occurrence of this systemic adverse event are strongly suggestive of a causal relationship in the present case. Although systemic complications have been rarely associated with intravitreal injections of anti-VEGF agents, physicians should be aware that novel adverse events can still occur in AMD patients treated with anti-VEGF agents.

Two Cases of Acute Abdomen after an Intravitreal Injection of Bevacizumab

Yasutaka Onoda, Tomoaki Shiba, Yuichiro Hori, Takatoshi Maeno, Mao Takahashi

1Department of Ophthalmology, and 2Cardiovascular Center, Toho University Sakura Medical Center, Chiba, and 3Department of Ophthalmology, Toho University School of Medicine, Tokyo, Japan

Key Words

Intravitreal injection of bevacizumab - Acute abdomen - Side effect - Vascular endothelial growth factor - Ischemic colitis - Paralytic ileus

Abstract

We report on a patient with ischemic colitis and another with paralytic ileus, both of whom experienced an acute abdomen after intravitreal injection of bevacizumab (IVB). Case 1 was a 78-year-old woman. Her medical history included surgery for colon carcinoma 10 years earlier. The patient developed acute severe abdominal pain and nausea the day after IVB for retinal vein occlusion with macular edema, and massive lower gastrointestinal bleeding occurred. Ischemic colitis was diagnosed. Case 2 was a 68-year-old man who presented with neovascular glaucoma with proliferative diabetic retinopathy. We performed vitreous surgery on the 9th day after IVB, and we reperformed IVB at the end of the vitreous surgery. On the first postoperative day, severe abdominal distension, vomiting and abdominal pain were observed, and paralytic ileus was diagnosed. It is possible that gastrointestinal disorders are induced after IVB, depending on the patient’s background, including for example severe diabetes or a history of surgery for gastrointestinal cancer. Thus, ophthalmologists should apply alternative therapies instead of IVB to patients with severe diabetes mellitus or a history of gastrointestinal cancer.
The pharmacovigilante’s dilemma

A signal should be identified as soon as possible to allow early warning

but

When is there ENOUGH evidence?
“What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

What do we have so far?

“What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

Clinical Characterization #1: Is the drug used in the real world?

Optum Extended SES (v876) Drug Era Report

<table>
<thead>
<tr>
<th>Concept Id</th>
<th>Name</th>
<th>Person Count</th>
<th>Prevalence</th>
<th>Length of Era</th>
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<tr>
<td>45775396</td>
<td>nintedanib</td>
<td>1,760</td>
<td>0.00%</td>
<td>218.10</td>
</tr>
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</table>

Showing 1 to 1 of 1 entries (filtered from 1,911 total entries)
Clinical Characterization #1: Is the drug used in the real world?

nintedanib Drilldown Report

Prevalence

MALE | FEMALE | UNKNOWN

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</table>

Year of Observation
Clinical Characterization #2:
How many patients are newly exposed?

Inclusion Report for Optum Extended SES (v876)

<table>
<thead>
<tr>
<th>Inclusion Rule</th>
<th>N</th>
<th>% Satisfied</th>
<th>% To-Gain</th>
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<tbody>
<tr>
<td>1. does not have prior colitis</td>
<td>1,127</td>
<td>93.84%</td>
<td>6.16%</td>
</tr>
</tbody>
</table>

Summary Statistics:
- Match Rate: 93.84%
- Matches: 1,127
- Total Events: 1,201
Clinical characterization #3:
Who are these patients?
Clinical characterization #4: What is the incidence of the event?

### Optum Panther (v811)

<table>
<thead>
<tr>
<th>Summary Statistics:</th>
<th>Persons</th>
<th>Cases</th>
<th>Proportion [+]/- per 1k persons</th>
<th>Time At Risk (years)</th>
<th>Rate [+]/- per 1k years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,071</td>
<td>16</td>
<td>14.94</td>
<td>282</td>
<td>56.74</td>
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</table>

<table>
<thead>
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<th>Stratify Rule</th>
<th>N</th>
<th>Cases</th>
<th>Proportion [+]/- per 1k persons</th>
<th>Time At Risk (years)</th>
<th>Rate [+]/- per 1k years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. gender = Female</td>
<td>390</td>
<td>6</td>
<td>15.38</td>
<td>105</td>
<td>57.14</td>
</tr>
<tr>
<td>2. age &gt; 70</td>
<td>636</td>
<td>13</td>
<td>20.44</td>
<td>163</td>
<td>79.75</td>
</tr>
<tr>
<td>3. Initial drug strength is 150mg</td>
<td>996</td>
<td>13</td>
<td>13.05</td>
<td>261</td>
<td>49.81</td>
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<tr>
<td>4. Initial drug strength is 100mg</td>
<td>82</td>
<td>3</td>
<td>36.59</td>
<td>27</td>
<td>111.11</td>
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</tbody>
</table>
Population-level effect estimation:
Design a comparative cohort analysis
Population-level effect estimation: Apply multiple methods, multiple databases, and negative controls to assess consistency of results

<table>
<thead>
<tr>
<th>Design</th>
<th>Database</th>
<th>Target</th>
<th>Comparator</th>
<th>Outcome</th>
<th>IRR</th>
<th>LB95</th>
<th>UB95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-controlled cohort, on-treatment</td>
<td>Optum</td>
<td>Nintenanib</td>
<td>Pre-exposure</td>
<td>Colitis</td>
<td>12.28</td>
<td>3.05</td>
<td>107.25</td>
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<tr>
<td>Self-controlled cohort, on-treatment</td>
<td>MDCR</td>
<td>Nintenanib</td>
<td>Pre-exposure</td>
<td>Colitis</td>
<td>2.58</td>
<td>0.74</td>
<td>11.25</td>
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<tr>
<td>Self-controlled cohort, on-treatment</td>
<td>MDCR</td>
<td>Pirfenidone</td>
<td>Pre-exposure</td>
<td>Colitis</td>
<td>0.50</td>
<td>0.13</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Negative control exposure?

Different database?

Different analysis method?

Preliminary findings subject to review and additional analysis
Population-level estimation: following best practices for diagnostic evaluation as we should do with any protocol-based assessment.
How can real world evidence help?

“What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

“Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rule of evidence that must be obeyed before we can accept cause and effect... What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”
Patient-level prediction:
Which patients will experience the outcome?
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Do you have an idea for an AI solution that predicts health outcomes while building trust and transparency with clinicians and patients?