Background: The nocebo phenomenon, the opposite of placebo, defined as negative changes in a patient's symptoms or condition resulting from negative expectations to treatment and possibly leading to suboptimal outcomes and non-adherence, is more frequent than previously thought in rheumatology practice[1]. The tyrosine kinase inhibitor nintedanib has shown efficacy for the treatment of systemic sclerosis (SSc)-associated interstitial lung disease in SENSCIS, a recent randomized controlled trial (RCT)[2]. Diarrhoea was the most frequently reported adverse event in SENSCIS.

Objectives: To test whether the nocebo phenomenon is involved in the prevalence of diarrhoea as an adverse event in trials with nintedanib.

Methods: We compared the incidence of diarrhoea in the placebo arm between SENSCIS and all other placebo controlled RCTs involving >40 SSc patients in the placebo arm and 76% in the active treatment arm in SENSCIS. These numbers are comparing to a prevalence of only 7% (range 2.3-9.1%) and 9% (range 5.8-14%), respectively of other RCTs in SSc (bosentan, n=2; macitentan, n=2; tocilizumab, n=1). Since the estimated point prevalence of diarrhoea in an SSc cohort similar to SENSCIS would not exceed 15% based on the literature, there was an at least 2-fold increase in the occurrence of diarrhoea in the placebo group during SENSCIS. More importantly, when looking into other nintedanib RCTs and diarrhoea-related warnings in ICFs.

Results: The mean percentage of patients reporting diarrhoea at baseline was 20% and 18% in cancer and idiopathic pulmonary fibrosis (IPF) trials, respectively, which is almost half than in SENSCIS. Consistent with our hypothesis, the percentage of diarrhoea in the placebo arms of the different nintedanib RCTs increased along with the number of mentions and the number of lines devoted to "diarrhoea" in the respective ICFs.

Conclusion: These results indicate that the nocebo phenomenon is partially involved in the high prevalence of diarrhoea among SSc patients participating in the SENSCIS trial. Whether patients with SSc have increased susceptibility to the nocebo phenomenon when compared to patients with IPF or cancer deserves further study.

References:

Disclosure of Interests: Vasiliki-Kalliopi Bournia Grant/research support from: Travel Grant from Boehringer Ingelheim, Dimos Mitsikostas: None declared, Oliver Distler Grant/research support from: Grants/Research support from: Actelion, Bayer, Boehringer Ingelheim, Competitive Drug Development International Ltd. and Mitsubishi Tanabe; he also holds the issued Patent on nir-29 for the treatment of systemic sclerosis (US2074389, EP2331143)., Consultant of: Consultancy fees from Actelion, Acceleran Pharma, AnMar, Bayer, Baecon Discovery, Blade Therapeutics, Boehringer, CSL Behring, Cat-enion, ChemonAb, Curzon Pharmaceuticals, Ergonex, Galapagos NV, GSK, Glenmark Pharmaceuticals, Inventa, Italfarmaco, Iviv, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Roche, Sanofi and UCB, Speakers bureau: Speaker fees from Actelion, Bayer, Boehringer Ingelheim, Medscape, Pfizer and Roche, Petros Stikakis Grant/research support from: Grant/research support from: Abvie, Novartis, MSD, Actelion, Amgen, Pfizer, Janssen Pharmaceutical, UCB

DOI: 10.1136/annrheumdis-2020-eular.5245

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**Table 1. Percentage of patients developing diarrhoea in phase III nintedanib RCTs and diarrhoea-related warnings in ICFs**

<table>
<thead>
<tr>
<th>Published RCT (year of publication)</th>
<th>Treatment indication</th>
<th>placebo arm, N</th>
<th>nintedanib arm, N (mg/bid)</th>
<th>Adjunctive treatment</th>
<th>% Diarrhoea</th>
<th>Mentions of diarrhoea/lines devoted in ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSCIS (2019)</td>
<td>SSc-ILD</td>
<td>288 (150)</td>
<td>288 (150)</td>
<td>48% MMF 15% MTX 18% p from biologics, DMARDS, corticoids</td>
<td>31.6</td>
<td>75.7</td>
</tr>
<tr>
<td>INBUILD (2019)</td>
<td>Progressive Fibrosing ILD including SSc-ILD and other CTD-ILDs</td>
<td>331 (150)</td>
<td>332 (150)</td>
<td>21% corticosteroids 21% corticosteroids</td>
<td>23.9</td>
<td>66.9</td>
</tr>
<tr>
<td>INPULSIS1 (2014)</td>
<td>IPF</td>
<td>204 (150)</td>
<td>309 (150)</td>
<td>21% corticosteroids 21% corticosteroids</td>
<td>18.6</td>
<td>61.5</td>
</tr>
<tr>
<td>INPULSIS2 (2014)</td>
<td>IPF</td>
<td>219 (150)</td>
<td>329 (150)</td>
<td>21% corticosteroids 21% corticosteroids</td>
<td>18.3</td>
<td>63.2</td>
</tr>
<tr>
<td>LUME-Lung 1 (2014)</td>
<td>Lung cancer</td>
<td>659 (200)</td>
<td>655 (200)</td>
<td>dextacelix</td>
<td>21.8</td>
<td>42.3</td>
</tr>
<tr>
<td>LUME-Lung 2 (2016)</td>
<td>Lung cancer</td>
<td>360 (200)</td>
<td>353 (200)</td>
<td>pemetrexed</td>
<td>15.4</td>
<td>34.9</td>
</tr>
<tr>
<td>LUME-meso phase III</td>
<td>Pleural mesothelioma</td>
<td>229 (200)</td>
<td>229 (200)</td>
<td>pemetrexed &amp; cisplatin</td>
<td>23.0</td>
<td>53.0</td>
</tr>
</tbody>
</table>

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**AB0554 CONCORDANCE IN THE CLASSIFICATION CRITERIA IN A PATIENT COHORT WITH IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM).**

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Background: Different classifications criteria for IIM exist. New classification criteria are superior to previous in capturing different subgroups of IIM.

Objectives: To compare the concordance and disparity of Bohan and Peter and EULAR/ACR 2017 classification criteria at the level of diagnostic certainty, in a group of chilean patients with IIM.

Methods: 40 adults patients with IIM (27 Dermatomyositis (DM) and 13 Polymyositis (PM)), according Bohan and Peter criteria were analized. The patients were reclassified with EULAR/ACR criteria. The level of diagnostic certainty (definitive, probable and possible) was registered for both Classification Criteria. The concordance and disparity between criteria was evaluated. Concordance and disparity analysis were made considering the strict agreement between level of certainty of both criteria, using Cohen’s Kappa coefficient. The analysis was done for the complete cohort and for separated groups.

Patients with discordance belonging to the same subgroup were evaluated using contingency tables. The direction of the change (gain or loss of certainty) and the relation with diagnostic subgroup was also analyzed. Descriptive statistics is expressed as diagnostic categories, number of patients and rates.

Results: For the complete cohort and for DM and PM groups the concordance was low. For 27 patients with DM, the observed concordance rate was 63% (16 definitives, 1 probable). The observed disparity rate was 37%. The direction of the change was gain of one level of certainty in 14.5% and two levels in 22.2% of patients applying EULAR/ACR criteria compared to Bohan y Peter criteria. For 13 patients with PM, the observed concordance rate was 46% (3 definitives and 3 probables). The observed disparity rate was 54%. The direction of the change was loss of certainty. The loss of certainty was one level in 85.7% (one patient change from probable to possible). Only one patiente had gain of certainty of one level (14.3%).

Conclusion: The strict concordance between both classification criteria was low. The observed concordances were better in patients with DM that PM. The disparities involved gain of level of diagnostic certainty in DM patients, while in PM patients there was mostly lost of level of certainty.

References:

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5662

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