AB0553

THE NOCEBO PHENOMENON PARTLY ACCOUNTS FOR DIARRHOEA AMONG PARTICIPANTS IN THE RANDOMIZED PLACEBO-CONTROLLED TRIAL OF NINTEDANIB FOR INTERSTITIAL LUNG DISEASE ASSOCIATED WITH SYSTEMIC SCLEROSIS (SENSCIS)

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Background: The nocebo phenomenon, the opposite of placebo, defined as unfavourable changes in a patient's symptoms or condition resulting from negative anticipations 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 each arm, as well as between SENSCIS and all other nintedanib RCTs published so far. We also compared the strength of the warnings for diarrhea (ie times word is mentioned and number of lines devoted to nintedanib related "diarrhoea") in the informed consent forms (ICFs) of different nintedanib RCTs

Results: The mean percentage of patients reporting diarrhoea was 32% 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 (Table 1), we found that patients reporting diarrhoea in the placebo arm were 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.

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

Published RCT (year of publication)	Treatment indication	placebo arm, N	nintedanib arm, N (mg/bid)	Adjunctive treatment	% Diarrhoea		Mentions of 'diarrhoea' / lines devoted in ICF
					Placebo	Active treatment	
SENSCIS (2019)	SSc-ILD	288	288(150)	48% MMF 5% MTX	31.6	75.7	9/11
INBUILD (2019)	Progressive Fibrosing ILD including SSc-ILD and other CTD-ILDs	331	332 (150)	18% ≥1 from biologics, DMARDs, corticoids	23.9	66.9	8/10
INPULSIS1 (2014)	IPF	204	309 (150)	21% corticosteroids	18.6	61.5	3/3
INPULSIS2 (2014)	IPF	219	329 (150)	21% corticosteroids	18.3	63.2	3/3
LUME-Lung 1 (2014)	Lung cancer	659	655(200)	docetaxel	21.8	42.3	2/4
LUME-Lung 2 (2016)	Lung cancer	360	353(200)	pemetrexed	15.4	34.9	4/5
LUME-meso phase III (2019)	Malignant pleural mesothelioma	229	229(200)	pemetrexed & cisplatin	23.0	53.0	4/5

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:

[1] Kravvariti E et al. *Nat. Rev. Rheumatol.* 2018;14:727.

[2] Distler O et al. *N. Engl. J. Med.* 2019;380:2518.

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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 to Bohan and Peter criteria were analyzed. 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 patient 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 than PM. The disparities involved gain of level of diagnostic certainty in DM patients, while in PM patients there was mostly loss of level of certainty.

References:

[1] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *NEJM* 1975;292:344-7.

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