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Research letter

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Diarrhoea in Systemic Sclerosis Patients as a Nocebo Effect of Nintedanib

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Introduction

Nocebo effects, the opposite of placebo effects, are defined as unfavourable changes in a patient's symptoms or condition occurring due to negative anticipation and possibly leading to suboptimal outcomes via treatment discontinuation or non-adherence[1]. Symptoms most commonly associated with nocebo in both dedicated neurobiological research and randomized controlled trial (RCT) settings are non-specific complains such as pain, malaise, dizziness, or gastrointestinal upset[2]. Despite evidence highlighting the implications of placebo and nocebo effects on daily practice and RCT design and interpretation, determining their true frequency and intensity remains a challenge[1, 2].

Herein, we tested the hypothesis that nocebo partly accounts for diarrhoea among participants in the SENSCIS RCT of nintedanib for systemic sclerosis (SSc)-associated interstitial lung disease (ILD)[3]. Nintedanib is a tyrosine kinase inhibitor, currently approved for the treatment of idiopathic pulmonary fibrosis (IPF)[4], chronic fibrotic ILD with a progressive phenotype[5, 6], ILD associated with SSc[3], and as second-line agent for locally advanced metastatic or recurrent non-small cell lung cancer[7, 8]. Diarrhoea was the most frequently reported adverse event in SENSCIS, with a mean rate of 32% in the placebo and 76% in the nintedanib arm.

Methods

We searched PubMed to identify all placebo controlled RCTs performed in SSc, which included more than 40 patients in each arm and reported the rate of diarrhoea as an adverse event in the placebo group and compared it with the respective rate of SENSCIS. Next we identified all phase III placebo controlled RCTs of nintedanib published so far and compared the rates of diarrhoea reported for the placebo group. We also compared the strength of the warnings for diarrhoea in the English version of the informed consent forms (ICFs) of the different nintedanib RCTs by counting the number of times the word "diarrhoea" is mentioned and the number of lines devoted to "diarrhoea" in relation to nintedanib.

Results

Only a mean of 7% (range 2.3-9.1%) of patients reported diarrhoea in the placebo arm of trials investigating bosentan (RAPIDS-1[9] and RAPIDS-2[10]) or macitentan (DUAL-1 and DUAL-2[11]) for the prevention of new digital ulcers, or tocilizumab for skin fibrosis (faSScinate[12]), compared to the respective 32% in the SENCSIS placebo arm.

As shown in the **Table,** the rate of patients reporting diarrhoea in the placebo arm of SENSCIS was nearly double compared to the other RCTs of nintedanib in cancer (LUME-LUNG-1 and -2, p=0.000031, chi-square test)[7, 8, 13] and IPF (INPULSIS-1 and -2)[4] (p=0.000052, chi-square test) trials. Consistent with our hypothesis, the rate of diarrhoea in the placebo arms of the different nintedanib RCTs correlated significantly with the number times the word "diarrhoea" was mentioned (Pearson's r=0.756, p=0.049), the number of lines devoted to "diarrhoea" in the respective ICFs (r=0.799, p=0.031) and with the sum of these two figures (r=0.785, p=0.037).

Notably, since diarrhoea during the screening period of SENSCIS was reported by 9.7% of patients in the placebo group and 10.8% of patients in the nintedanib group (BI data on file, with permission), there was a nearly4-fold increase of diarrhoea in the placebo group during the first weeks of the trial[14]. Likewise, the rates of diarrhoea in the placebo group were 1.4% at screening versus 18.4% during the 52-week treatment period for INPULSIS-1 and -2, 2.4% versus 23.9% for INBUILD, 0.3% versus 21.8% for LUME-Lung-1, 1.7% versus 15.4% for LUME-Lung-2 and 0 versus 23.2% for LUME-Meso, respectively. By contrast, such findings were not evident in other RCTs in SSc. In the faSScinate study diarrhoea reports in the placebo group increased from 6.8% at screening to only 9.1% after 48 weeks of tocilizumab treatment. In the RAPIDS-1 and RAPIDS-2 trials these figures decreased from 7% and 10% at baseline to 2.3% and 8.9% after 16 weeks of bosentan treatment, whereas in the DUAL-1 and DUAL-2 studies, the point-prevalence of diarrhoea at screening increased from 1% and 0% respectively to 7.2% and 6.7% respectively, after 16 weeks of macitentan treatment (data with permission).

Discussion

Our results imply that nocebo effects are partially involved in the high prevalence of diarrhoea among SSc patients participating in SENSCIS, and possibly also in the INBUILD RCTs of nintedanib. The most compelling evidence in support of our hypothesis rests with the observation that the percentage of diarrhoea in the placebo group of SENSCIS was much lower prior to and nearly quadrupled following initiation of the study. An equally impressive increase in diarrhoea reports relative to pre-treatment was also observed in the placebo groups of the INBUILD, INPULSIS and LUME trials, alluding to a notable, albeit less pronounced nocebo effect also in the trials of nintedanib for indications other than SSc. Congruently, the vast majority of diarrhoeal events observed in SSc SENSCIS participants were of mild or moderate severity (67% and 30% respectively in the placebo group), as one would expect for nocebo-related diarrhoea[14].

Interestingly, IPF and cancer patients receiving nintedanib in the INPULSIS and LUME trials respectively, displayed significantly lower diarrhoea rates in the placebo group compared to SSc patients participating in SENSCIS, despite the fact that cancer patients also received adjunctive chemotherapy with docetaxele, cisplatine and pemetrexed, known to cause diarrhoea as an adverse event. Diarrhoea is not uncommon in SSc, owing to the underlying mechanisms of carbohydrate malabsorption, intestinal hypomotility and secondary bacterial overgrowth; reports from observational SSc cohorts show a prevalence of diarrhoea between 5-25%[15, 16]. It is, therefore, possible that SSc patients, who have frequently experienced lower GI symptoms prior to their inclusion in a trial, are preconditioned to develop GI nocebo manifestations. On the other hand, in all other than SENSCIS RCTs included in our study involving SSc patients, diarrhoea in the placebo arm did not exceed 9%. Therefore, the herein presented evidence of an exaggerated nocebo effect in SENSCIS and also possibly in INBUILD might not necessarily be related to the SSc disease itself, but to procedures followed during the study.

Our study has some limitations. One could argue that SENSCIS cannot be compared to the other trials, since their duration differs, and any patient is more

likely to develop diarrhea at least once over a longer than over a shorter time period. Nevertheless, diarrhoea events clearly accumulate during the first 15 weeks in SENSCIS[14], a period which is covered in every other RCT used for comparison. Furthermore, methodological differences in the way diarrhoea was defined or recorded could have led to an information bias. In fact, rates of diarrhoea in the other SSc trials used here for comparison were much lower than the 5-25% prevalence of diarrhoea in SSc reported in the literature, possibly meaning that diarrhea, not being an adverse event of special interest, was not actively sought for in these trials. However, this 5-25% is a lifetime prevalence and should not be comparable to that observed during RCTs. Moreover, in none of the nintedanib trials was diarrhoea considered an adverse event of special interest, nor were any structured questionnaires used for its detection. Another limitation could be that, "pre-treatment" reports of diarrhoea are not always accurate, as patients who participate in RCTs are usually very enthusiastic and could mask their symptoms, so as not to reduce their opportunity to be recruited. Whether patients with SSc have an increased susceptibility to nocebo compared to patients with IPF or cancer deserves further study.

Obtaining informed consent prior to participation in RCTs is obviously obligatory. During this process, however, patients are exposed to information that largely shapes their anticipations regarding efficacy and side effects of the medication under investigation, potentially producing a nocebo effect[1, 2]. Accordingly, our data show that in the published RCTs of nintedanib, reporting of diarrhoea increases along with the strength of the warnings for diarrhoea in ICFs. Interestingly, recent evidence has shown that nocebo phenomena are reduced when informing trial participants about nocebo, personalizing the process of obtaining informed consent, selectively using "authorized concealment" of benign, non-specific side-effects and putting adverse events in a positive frame[17]. Therefore, improving the way informed consent is obtained and investing in doctor-patient relationship may be needed in future RCTs.

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Table. Percentage of patients developing diarrhoea in phase III nintedanib RCTs and diarrhoea-related warnings in ICFs. Percentages of patients reporting diarrhoea in the placebo group of these trials correlated positively with the number of mentions of "diarrhoea" in the respective ICFs (Pearson correlation, r=0.756, p=0.049), the number of lines devoted to nintedanib related diarrhoea in the respective ICFs (r=0.799, p=0.031) and the sum of mentions and number of lines devoted to diarrhoea (r=0.785, p=0.037).

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)	48.4% 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

RCT: Randomized Controlled Trial, ICF: Informed Consent Form, SSc: Systemic Sclerosis, ILD: Interstitial Lung Disease, CTD-ILD: Connective Tissue Disease associated Interstitial Lung Disease, IPF: Interstitial Lung Disease, MMF: Mycophenolate mophetil, MTX: methotrexate, DMARDs: Disease Modifying Antirheumatic Drugs.