EFFICACY AND TOLERABILITY OF THE PROBIOTIC VSL#3 FOR THE TREATMENT OF PATIENTS WITH FIBROMYALGIA AND ASSOCIATED GASTROINTESTINAL SYMPTOMATOLOGY; A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL.

ClinicalTrials.gov ID: NTC042566785, updated 02/04/2020

Investigators:

Elena P. Calandre (PI), Institute of Neurosciences, Universidad de Granada, Granada, Spain
Fernando-Rico-Villademoros, Cociente, Madrid, Spain
Javier Hidalgo Tallón, Clinica Menorca, Granada, Spain
Rocío Molina Barea, Clínica Menorca. Granada, Spain
Cristina Molina Hidalgo, Clínica Menorca, Granada, Spain
Mª Dolores Carrillo Izquierdo, Universidad Católica de Murcia, Spain

INTRODUCTION

Fibromyalgia is a complex syndrome. Although its main characteristic is chronic generalized musculoskeletal pain, in most patients it is accompanied by other symptoms, the most common of which are non-restorative sleep, chronic fatigue, cognitive difficulties and anxious and/or depressive symptoms.[1] It is included within the central sensitization syndromes with which it shows a high comorbidity.[2]

The first diagnostic criteria for fibromyalgia were established by the American College of Rheumatology in 1990[3] and were based essentially on the palpation of tender points without paying attention to the associated symptomatology. These criteria were subsequently modified in 2010, eliminating the need for palpation to record the relationship of tender body areas and adding a scale of symptom severity;[4] in 2011, these criteria were simplified to allow self-assessment by patients.[5] Finally, a new review was conducted in 2016 that slightly modified specifications for the Widespread Pain Index (WPI) and Symptom Severity Score (SSS).[6]

Among the symptoms frequently associated with fibromyalgia, gastrointestinal symptoms are very common. In fact, in the specific case of one of the comorbid pathologies of fibromyalgia, irritable bowel syndrome (IBS), the prevalence of fibromyalgia has been estimated to range from 20 to 65% with a mean value of 41%.[2] On the other hand, even among patients with fibromyalgia who do not meet criteria to diagnose IBS, the presence of gastrointestinal symptomatology is frequently observed.[7] The cause of these symptoms is unknown although in two previous publications it was suggested that they could be due to intestinal bacterial overgrowth.[8-9] An unpublished study by our team found that, in comparison with controls, patients with fibromyalgia presented a clear alteration of the intestinal fermentation processes, although it could not be affirmed that this was due to bacterial overgrowth or other type of intestinal dysbiosis. A very recent study in patients with chronic fatigue syndrome, a pathology that shows a broad overlap with fibromyalgia, has found the presence of intestinal dysbiosis in these patients.[10]

No specific treatment has been studied to alleviate the gastrointestinal symptoms associated with fibromyalgia despite their frequency and their being mentioned by most of the patients as extremely annoying. This may explain the frequency with which these patients resort to diets of one type or another even though their benefits have not been demonstrated previously.[11] In this regard, the use of probiotics, alone or associated with prebiotics (synbiotics), could be an interesting therapeutic approach since the use of these products is advocated as an important alternative for the treatment of chronic pathologies of the gastrointestinal tract.[11-12]

More concretely, the use of probiotics on the management of IBS has been recently revised in a metanalysis that found that the use of these products is effective to improve the symptoms of IBS, although more information is required to assess which individual species and strains are the most effective[13]. Among the different probiotics tested VSL#3 has shown some promising results in the treament of IBS both in adults and in children[14-16]. VSL#3 is a polymicrobial probiotic combination product that includes multiple strains of three lyophillized bacteria species: *bifidobacterium, lactobacillus,* and *streptococcus*. It is available in sachets contanining 450 billions of bacteria in powder form.

Considering both the frequency of comorbidity between fibromyalgia and IBS, as well as the frequent presence of non-specific gastrointestinal symptoms in patients with fibromyalgia who might be susceptible to be treated with probiotics, the objective of this trial is to assess the efficacy and tolerability of VSL#3 in patients with fibromyalgia and gastrointestinal symptomatology.

SUBJECTS AND METHODS

Inclusion criteria:

- To have been diagnosed with fibromyalgia, diagnosis that will be confirmed at the time of beginning the screening of patients using the ACR 2016 criteria (Wolfe 2016)
- 18 years of age or older.

- Agreement to voluntarily participate in the study by signing informed consent.
- Be willing to, and do not need under medical criteria, to modify the treatment previously received for fibromyalgia, both of pharmacological and non-pharmacological type, and not change the habits of life, especially about the habitual diet, during the trial's duration
- To regularly suffer (two or more times by week) from three or more of the following symptoms: abdominal pain, abdominal bloating, meteorism, flatulence, nausea, dyspepsia, eructation, constipation and/or diarrhea.

Exclusion criteria:

- To suffer severe mental illness other than major depression.
- To suffer severe renal, hepatic or cardiovascular organic disease that, at the discretion of the investigator, could interfere the participation in the study.
- To suffer any chronic gastrointestinal disease other than irritable bowel syndrome such as inflammatory bowel disease, active gastroduodenal ulcer or colorectal carcinoma.
- Pregnancy or breastfeeding.

Outcome variables:

The severity of the following types of gastrointestinal symptoms: abdominal pain, abdominal bloating, meteorism, flatulence, constipation, diarrhea, nausea, eructation, and dyspepsia will be evaluated using a Visual Analogue Scale (VAS).

The primary endpoint will be the mean severity of the three main gastrointestinal symptoms reported by patients with fibromyalgia, i.e. abdominal pain, abdominal bloating and meteorism.

A seven points, Likert-type scale, the Patient Global Improvement Scale (PGI) will be used to assess the relief of patients' general symptomatology.

Fibromyalgia Impact Questionnaire Revised (FIQR). This instrument was created to assess the overall symptoms related to fibromyalgia,[17] a modified version having been created in 2009;[18] the validated Spanish version will be used.[19] The total score of the FIQR, assessed through various visual analogue scales, ranges from 0 to 100, and the higher the score, the greater the severity of fibromyalgia. It will allow checking whether an eventual improvement in the gastrointestinal symptoms is reflected in a smaller impact of the symptomatology associated with fibromyalgia.

Insomnia Severity Inventory (ISI). It is a brief questionnaire, composed of seven items evaluated on Likert-type scales, which allows assessing the severity of insomnia. Its total score can range from 0 to 28 points; the higher the score obtained, the greater the severity of insomnia. Since poor sleep quality is also a symptom frequently associated with fibromyalgia it will be used to check whether an eventual improvement in gastrointestinal symptoms is reflected in a better quality of sleep. The validated Spanish version of the questionnaire will be used.[20]

9-item Patient Health Questionnaire (PHQ-9). It is a brief questionnaire whose objective is to evaluate depressive symptoms. It consists of 9 items evaluated using Likert-type scales. Its total score ranges from 0 to 27 points: the higher the score reached, the greater the severity of the depression. Since depression is also a symptom frequently associated with fibromyalgia it will be used to check whether an eventual improvement in gastrointestinal symptoms is reflected in an improvement in depressive symptomatology. A validated Spanish version of the questionnaire will be used.[20]

Short-Form Health Survey SF-36. It is multi-item generic health survey intended to evaluate general health concepts not specific to any age, disease or treatment group. It measures 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health that can also be condensed in two summary mesures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The validated Spanich version will be applied[24].

Study development:

The period between the initial recruitment of patients and their entry into the trial will be two weeks; during this period, the subjects' suitability to be included in the study will be assessed.

The treatment will consist of the intake of 1 sachet of VSL#3 or matching placebo twice a day during 12 weeks. The assignment of the subjects to the group that will receive the active product or the placebo will be randomized.

On the day of initiation of treatment, the following questionnaires will be administered: VAS of abdominal pain, abdominal bloating, meteorism, flatulence, constipation, diarrhea, nausea, eructation and dyspepsia, FIQR, ISI, PHQ-9, PGI and SF-36.

VAS of gastrointestinal symptomatology will be filled weekly by the patients during the first 4 weeks of the trial and every 2 weeks between weeks 4 and 12 of the trial. At week 12, FIQR, ISI, PHQ-9 and quality of life questionnaire will also be completed again. PGI will be filled on weeks 4, 8, and 12.

At the end of the treatment period, patients will be monitored at 4, 12 and 24 weeks thereafter; these visits will measure VASs of gastrointestinal symptoms, FIQR, PGI and SF-36.

Adverse effects potentially associated with treatment will be collected at each visit through an open question system. Also, during the 12 weeks of treatment the medication packages will be collected to control therapeutic compliance.

Calculation of sample size and assessment of results

Given the absence of previous intervention studies in this area and, in general, limited information on this aspect of fibromyalgia, this should be considered a pilot study. To this consideration should be added the limitation as to the recruitment of patients by the participating sites. Thus, the calculation of the sample size is based on the feasibility of recruiting them. The recruitment of 120 patients has been estimated as a reasonable attainable goal.

The results obtained will be analyzed by applying the Student t test for independent samples to compare the data between the subjects who received placebo and those who received active product and with a two-way analysis of variance to compare the data in the subgroups of patients treated with placebo and with VSL#3..

References:

1. Clauw DJ. Fibromyalgia and related conditions. Mayo Clin Proc 2015; 90:680-692.

2. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat 2012; 2012:584373.

3. Wolfe F, Smythe HA, Yunus MD, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990; 33:160-172.

4. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010; 62:600-610.

5. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38:1113-22

6. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 revisions of the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016; 46:319-329.

7. Slim M, Calandre EP, Rico-Villademoros F. An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms. Rheumatol Int 2015; 35:561-567.

8. Pimentel M, Chow EJ, Hallegua D, Wallace D, Lin HC. Small intestinal bacterial overgrowth: A possible association with fibromyalgia. J Musculoskelet Pain 2001; 9:105-113.

9. Pimentel M, Wallace D, Hallegua D *et al.* A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Dis 2004; 63: 450-452.

10. Nagy-Szakal D, Williams BL, Mishra N, et al. Fecal metagenomic profiles in subgroups of patients with myalgi encephalomyelitis/chronic fatigue syndrome. Microbiome 2017; 5:44.

11. Arranz LI, Canela MA, Rafecas M. Dietary aspects in fibromyalgia patients: results of a survey on food awareness, allergies, and nutritional supplementation. Rheumatol Int 2012;32:2615-21.

12. 12. López-Rodriguez MM. Granero Molina J, Férnandez Medina IM, et al. Patrones de evitación y conductas alimentarias en pacientes con fibromialgia. Endocrinol Diabetes Nutr 2017 [epub ahead of print].

13. Bull MJ, Plummer MT. Part 2. Treatments for chronic gastrointestinal disease and gut dysbiosis. Integr Med 2015; 14:25-33.

13. Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and metaanalysis. Am J Gastroenterol 2014; 109-1547-1561.

14. Kim HJ et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome.
Aliment Pharmacol Ther. 2003 Apr 1;17(7):895-904.

15. Kim HJ, Vazquez-Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL#3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil 2005; 17:687-696.

16. Guandalini S, Magazzù G, Chiaro A, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gasteoenterol Nutr 2010; 51:24-30.

17. García-Leiva JM, Carrasco JL, Slim M, et al. Celiac symptoms in patients with fibromalgia:a cross-sectional study. Rheumatol Int 2015; 35:562-567.

18. Calandre EP, Garcia-Leiva JM, Ordoñez-Carrasco J, et al. Gastrointestinal symptomatology and intestinal fermentation in patients with fibromyalgia. Clin Rheumatol (under review).

19. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005; 23 (5 suppl. 39):S-154-S162.

20. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire: validation and psychometric properties. Arthritis Res Ther 2009; 11:R120.

21. Salgueiro M, García-Leiva JM, Ballesteros J, et al. Validation of a Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQR). Health Qual Life Outcomes 2013; 11:132.

22. Fernández-Mendoza J, Rodríguez-Muñoz A, Vela-Bueno A, et al. The Spanish version of the Insomnia Severity Index: a confirmatory factor analysis. Sleep Med 2012; 13:207-210.

23. Baader T, Molina JL, Venezian S, et al. Validación y utilidad de la encuesta PHQ-9 (Patient Health Questionnaire) en el diagnóstico de depresión en pacientes usuarios de atención primaria en Chile. RevChil Neuro-Psiquiatr 2012; 50:10-22.

24. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. Med Clin (Barc) 1995; 104:771-776,