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Effect of Avemar® - a fermented wheat germ extract - on rheumatoid arthritis. Preliminary data

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ABSTRACT

Objective. *To investigate the effect of the fermented wheat germ extract (Avemar®) in patients with severe rheumatoid arthritis (RA).*

Methods. *Fifteen female RA (Steinbrocker II-III) patients, who had unsuccesfully tried two different DMARD treatments, were enrolled in an open-label, 1-year long, pilot clinical study. DMARD and steroid therapies were recorded and continued. All patients received Avemar® as additional therapy. For measurement of efficacy the Ritchie Index, the Health Assessment Questionnaire (HAQ) and the assessment of morning stiffness were applied. Patients were evaluated at baseline, 6 and 12 months. For statistical analyses the Wilcoxon test was used.*

Results. *At both 6 and 12 months, Ritchie index, HAQ and morning stiffness showed significant improvements compared with the baseline values. Dosages of steroids could be reduced in about half of the patients. No side effects of Avemar® were observed.*

Conclusion. *Supplementation of standard therapies with a continuous administration of Avemar® is beneficial for RA patients.*

Introduction

In the past years, a natural product, as a dietary food for special medical purposes (i. e. medical food) for cancer patients, has been approved by the health authorities of two EU countries (Hungary, Czech Republic). This medical food – called Avemar® – is a water soluble granulate which contains a standardized fermented wheat germ extract (FWGE) manufactured under good manufacturing practice (GMP) conditions in Hungary (1). Avemar® is the first original product with approved oncological indication, developed by Hungarians and, brought on the market after a pause of more than 30 years.

This medical food has been demonstrated to have supportive effects in the treatment of colorectal (2), oral cavity (1), head- and neck (3), breast (1) and lung (1) cancers, in skin melanoma (4) and, inhibited the development of febrile neutropenia in high-dose chemotherapy treated children (5). One of us (G.B.) observed that rheumatoid arthritis (RA) patients, who had concurrent cancer and were taking Avemar® on a continuous basis, showed surprisingly significant improvements in their RA symptoms. Therefore, a feasibility pilot clinical study with Avemar® in RA was carried out to test whether such patients could indeed benefit from taking this medical food.

Patients and methods

To be eligible for this study, patients had to have a severe RA according to the ACR (American College of Rheumatology) classification, and had to have either a stable disease with an insufficient outcome, or a progressive disease at least for three months prior to study entry. All patients had to previously failed at least two disease-modifying antirheumatic drug (DMARD) therapies due to either side effects or inefficacy. In all patients, at least one DMARD treatment had to be regarded as ineffective. If the ongoing DMARD treatment had been given for four consequtive months without any benefit, it was considered as ineffective. Exclusion criteria included: age less than 18, or more than 80 years; severe liver, kidney or hematological disorders; active gastric or duodenal ulcer; psychiatric disease or mental retardation. Patients were planned to continue their DMARD and steroid therapies, while receiving 2 x single dosage of Avemar® per day as additional therapy. A single dosage of the medical food contained 8.5 g pure FWGE plus arome and sweetener, prepared as a ready to drink mix shake and, should be consumed before meals. Measurement of efficacy: the Ritchie Index, comprising 52 joints, which is still considered a reliable tool of quantitative joint assessment (6) was used in this study. For the description of the patient reported outcomes, the Stanford Arthritis Center's Health Assessment Questionnaire (HAQ) (7) was employed. Morning stiffness assessment was carried out by using a rating scale (8). Laboratory (sedimentation rate, CRP, liver and kidney function tests) as well as hematological parameters (hemoglobin, hema-

tocrit) were obtained by standard procedures. Patients were evaluated at baseline and, 6 and 12 months afterwards. Ongoing DMARD and steroid therapies were recorded and continued. DMARD therapy was reduced if the Ritchie Index plus either the sedimentation rate or the CRP had been reduced by 20% at least for two months. For statistical analyses the Wilcoxon test, where $P < 0.05$ indicated a statistical significance, was used. Patients gave written informed consent, and the Regional Committee of the National Council of Health approved the protocol. The Declaration of Helsinki principles had been followed, and the patients were free to withdraw their consent at any time during the study.

Results

In Budapest, at the National Institute of Rheumatology and Physiotherapy, 15 refractory RA patients (ambulatory female patients; average age 54, range 44-68 years), whose disease was in Steinbrocker anatomical and functional categories of II and III, were enrolled in this open-label, non-randomized, pilot study. The average duration of their disease was 8.2 (range 3-25) years. All but one patient were seropositive. At the time of entry, 8 patients received DMARD (methotrexate/4, cyclosporine/3, chloroquine) plus corticosteroid (methylprednisolone/5, prednisolone/2, triamcinolone), while 2 patients received DMARD (methotrexate, sulfasalazine), and 3 patients received corticosteroid (methylprednisolone, prednisolone, dexamethasone) therapies alone.

By the end of the first 6 months of the study, the steroid dosage could be decreased in 5, and remained unchanged in 6 patients (significant change) (Fig. 1). By the end of the 12th months, it remained unchanged in 6, was decreased in 4, and was increased in 1 patient (not significant change). In 6 patients, the DMARD therapy remained unchanged during the whole study and, it was reduced in 3, increased in 1 patient (not significant change).

Compared to baseline data, the Ritchie index, the HAQ as well as the morning stiffness, all shown significant improvements by the end of the first 6th month of the trial and, these improvements have remained steady since then (Figs. 2-5). There were no consistent changes in the laboratory parameters. Though by the 6th month of the study a significant decrease in the sedimentation rate (from 46 to 28, $P = 0.033$) and a non-significant one in CRP (from 11 to 9, $P = 0.187$), indicators of systemic inflammation, could be detected, the values approached the baseline by the end of the study. During the 12 months treatment period no side effects of Avemar® were observed. Few patients complained of an unpleasant taste of the product, but no patients withdrew their consent due to this reason.

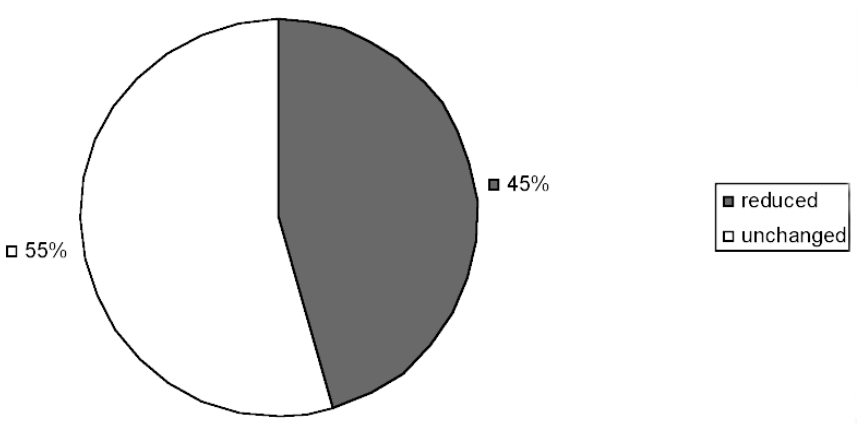

Fig. 1. Percentage of RA patients in whom the baseline corticosteroid dosages could be reduced after 6 months of supportive Avemar® treatment ($P = 0.031$).

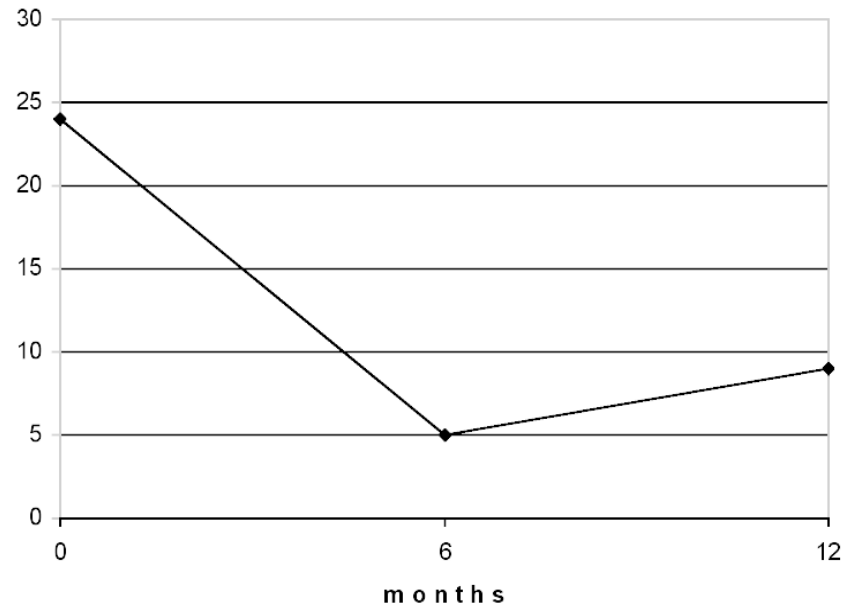

Fig. 2. Disease activity (Ritchie Index) in RA patients during 12 months of supportive Avemar® treatment ($z = 2.953$, $P = 0.003$).

Discussion

This is the first report on a wheat derived nutraceutical showing an adjunctive therapeutic effect in RA.

Although the mechanisms that contribute to the pathogenesis of RA are, at least partially, unknown, synovial macrophages and fibroblasts are now considered as targets for therapeutic intervention in RA, because insufficient apoptosis of these cells might contribute to the increased numbers of chronic inflammatory cells in RA joints and thus, to the persistence of the disease (9). Therefore, the resolution of chronic inflammation seems to require the apoptosis of effector cells, such as macrophages and synovial fibroblasts,

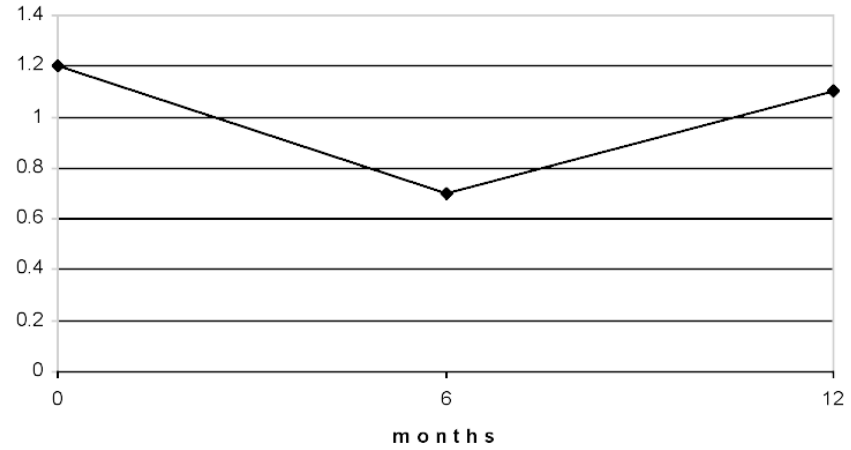

Fig. 3. Patient reported outcomes (HAQ) in RA during 12 months of supportive Avemar® treatment (z = 2.448, P = 0.014).

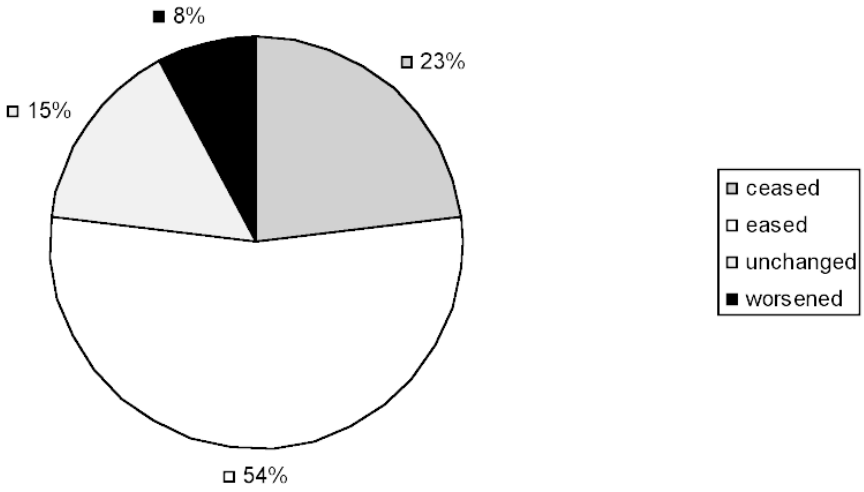

Fig. 4. Changes of morning stiffness in RA patients after 6 months of supportive Avemar® treatment (P = 0.009).

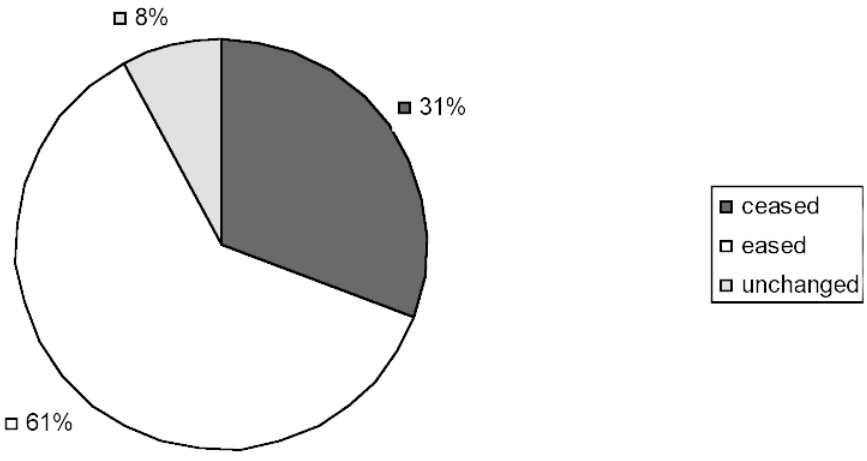

Fig. 5. Changes of morning stiffness in RA patients after 12 months of supportive Avemar® treatment (P = 0.002).

as well as activated synovial T cells, especially the selective depletion of subsets of T cells that recognize specific antigens. It has been established that an apoptotic pathway can be initiated through the activation of the caspase downstream proteases, including the cleavage of the poly(ADP-ribose) polymerase (PARP) enzyme, which is considered to be a hallmark of activation of caspase-3 like proteases during apoptosis, thus leading to genomic instabilities and disintegration in the target cells. Avemar® induced proteolysis of PARP shown by Western blots of extracts prepared from Jurkat leukemia cells treated with Avemar and probed with anti-PARP antibody (10). As this preparation has further been demonstrated to induce apoptosis in other cancer cell lines (11-13), it seems plausible to hypothesize its anti-RA efficacy by this mechanism. Recently, it has also been shown that Avemar® is a strong but, non-selective inhibitor of the cyclooxygenases 1 and 2 (14). In fact, for reasons we still do not know, on long term, however, we could not observe such anti-inflammatory manifestations in the values of the systemic inflammation-related macroscopic hematology parameters, such as in the sedimentation rate and CRP.

Previous oral toxicity studies showed that unlike corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), Avemar® does not exert any toxic effect (15). Since the benefits of this medical food have became steady during the 12 months long treatment in patients, whose former therapy with two DMARDs had otherwise failed, Avemar® could be implemented as a suitable adjunctive therapeutic tool in the treatment of RA.

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