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Can Standardized Plant Extracts Induce Complete Remission in Patients with Metastatic Tumors?

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Abstract

Background: The prognostic significance of malignant tumor-induced imbalance in the innate immune system is well known. The innate system uses a limited number of Pattern Recognition Receptors (PRR) to recognize conserved Pathogenic Associated Molecular Pattern (PAMP) structures expressed by microbes but not by host. PRR engagement often leads to the activation of natural immune cells which are important in the tumor defense. Growing evidence supports the hypothesis that similar to microbes various plant extracts can also contain PAMP-like structures which can activate cellular immune functions. Since the chemical production of PAMP structures is hardly accomplishable, the phytotherapy may be promising for the future tumor therapy. Objectives: The aim of this article is to present and discuss several favorable clinical responses of tumor patients treated with immunologically effective and standardized plant extracts (containing PAMP-like structures) as an addition to the conventional oncologic therapy.

Course of therapy and results: Two standardized plant preparations based on lectin-sugar interactions were the patients given. The dose of the active sugar-binding mistletoe lectin (ML), applied subcutaneously by standardized mistletoe extract (ME) preparations, was between 0.5 and 1.0 ng/kg and the dose of arabinoxylan (given by standardized rice bran preparation, MGN-3/Biobran) was between 12 and 45mg/kg twice a week. In addition, wheat germ extract (WGE) standardized for 2, 6-dimethoxy-p-benzoquinone (50-80 mg/kg Avemar four times a week) was also given which can sensitize tumor cells against natural immune effector cells. Case reports gave an account of complete or nearly complete remissions in patients with sarcoma or with hepatic metastases treated with these standardized plant immunomodulators with and without conventional oncologic therapy.

Conclusion: Standardized plant extracts (such as ME/ML, MGN-3 and WGE) seem to be potent candidates to be regarded as a supportive therapy of metastatic tumors.

Keywords: Tumor; Immune dysfunction; Plant immunomodulatory; Viscum album lectin; Rice brain preparation; Wheat germ extract

Introduction

Immunological background

In tumor patients the prognostic significance of natural immune functions was often established. It is now generally recognized that immunocompetent cells of the innate immune system are committed in two separate directions: (1) M1 macrophages and CD1a+ dentritic cells (DC1) generating IL-12 and other pro-inflammatory cytokines activating cytotoxic effector cells such as natural killer (NK) and natural killer T (NKT) cells, potent inhibitors of tumor growth; (2) prototypic M2 macrophages generating IL-4 and IL-10, which facilitate the generation of Th2 cells while inhibiting Th1 cells. In patients with malignant tumors both branches of innate immunity are often affected. The basic function of macrophages of the M2 type is to induce inflammation and promote cell proliferation by producing growth factors and through initiation of the arginase pathway, neoangiogenesis and tissue repair [3]. In the presence of malignancy, a higher than normal proportion of macrophages belongs to this prototypic M2 population and this appears to alter the balance of immune responses [5]. For example, in healthy individuals M2 monocytes were found to comprise only 10% of the total monocytic population, and in tumor patients this proportion was 40% higher [6].

Since many years, a beneficial influence of certain bacterial infections on the progress of tumor disease was often observed. Now, it is also clear that bacterial Pathogenic Associated Molecular Pattern (PAMP) molecules can stimulate the type 1 natural immune cells by binding the Pattern Recognition Receptors (PRR) on their membrane. However, in spite of the fact that the effects of a great number of bacterial preparations on tumor disease were investigated, there are not in clinical use. They have toxic side effects and in case of endotoxin a tolerance was also observed. Therefore the hypothesis is interesting that plants may also contain PAMP like molecules without toxic side effects.

Immunomodulatory effect of mistletoe lectin (ML)

The effect of ML given subcutaneously by standardized mistletoe extracts (ME) based on lectin –carbohydrate interaction on cell membrane of several immunocompetent cells of the innate immune system [7-10]. ML can selectively bind type-1 phagocytic cells and activates the "cascade"of cellular responses in innate immune, including granulocytes, macrophages, dentritic cells and natural killer (NK) cells. There is evidence accumulating that ML may also act as PAMP ligands and their binding to PRR on phagocytes shows some similarity with interactions between Toll-like receptors and PAMP ligands of microorganisms. Preclinical investigations in the tumor models (using nude mice xenotransplanted with human leiomyosarcoma and IL-12 deficient C57BL6 mice) show that without immunological reactions ML induce less anti-tumor efficacy [11]. ML, functioning as ligands for pattern recognition receptors of the natural immune system, is docked to ganglioside molecules (CD75) of monocytes and granulocytes, thereby stimulating the natural anti-tumor mechanisms. Through this interaction, ML is capable of partially restoring the immune imbalance in tumor patients [11-12].

Immunomodulatory effect of arabinoxylan concentrate

Similar to mistletoe lectin, modified arabinoxylan preparation obtained from rice bran (MGN-3/BioBranR) was also found to stimulate type-1 cells in the innate immune system and Arabinoxylan isolated cautiously from rice bran may also exhibit (similar to mistletoe lectin) PAMP-like properties. Arabinoxylan given by MGN-3/BioBranR increased NK cell activity both in vivo and in vitro [13] and enhanced phagocytic function of macrophages [14]. Given as combined therapy, mistletoe lectin and arabinoxylan appear to have an additive effect (unpublished data).

The effect of wheat germ extract

Wheat Germ Extract (WGE/AvemarR) containing 2, 6-dimethoxy-p-benzoquinone in 0.4 mg/g concentration as dry preparation [15]. Both in vitro and in vivo studies confirmed a significant antimetastatic effect by WGE [16-18]. The combination of WGE with NK stimulatory substances, such as ML in standardized mistletoe extracts and arabinoxylan in MGN3/BioBran is promising since WGE induces a down regulation in expression of major histocompatibility complex (MHC) class I proteins [19] and thus may have an additive effect to those of other immunomodulators. As known, the down regulation of MHC class I proteins reduce the effect of killing inhibitor receptors (KIR) resulting in enhanced killing of tumor targets by NK cells.

Material and methods

Standardized plant extracts

The application schema of standardized plant extracts used in treatment of patients is summarized in Table 1.

Iscador^{R} is a fermented aqueous mistletoe plant extract manufactured and supplied by Weleda AG (CH-4144 Arlesheim, Switzerland). The active (sugar-binding) lectin content of commercially available mistletoe extracts (Iscador M spec 5 mg) was measured in the research laboratory of Pharmacochemical Department of Medical University Pécs.

The determination of sugar binding Mistletoe Lectins (MLs) level in ME was carried out by an optimized ELLA technique as published previously [13]. Standardized ME exhibited a bell-shaped dose-response relationship and 0.5-1.0 ng/kg lectin doses were found to be most effective as it was always assessed previously using healthy volunteers. Since two and three therapy-free days were found to be necessary for an immunologically optimal effect, the subcutaneous ME injections were regularly given twice a week.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
ML in standardized ME	0.5-1.0 ng / kg s. c.			0.5-1.0 ng / kg s. c.			
MGN-3 standardized for Arabinoxylan	12-45 mg / kg per oral			12-45 mg / kg per oral			
WGE standardized for 2,6 dimethoxy p-benzoquinon	50-80 mg/kg per oral	50-80 mg/kg per oral		50-80 mg/kg per oral	50-80 mg/kg per oral		

Table 1: A schematic illustration of a proposed application of standardized plant extracts used as additive immunomodulatory treatment of patients with malignant tumors

The second immunomodulatory drug used in the combinative treatment of the presented patients is BioBran/MGN-3 which is manufactured and supplied by Daiwa Pharmaceutical Co, Ltd, Tokyo, Japan. BioBran/MGN-3 is composed of denaturated hemicellulose, which is obtained by rice bran hemicellulose reacting with multiple carbohydrate-hydrolyzing enzymes from shiitake mushrooms. BioBran/MGN-3 is standardized for its main chemical component: arabinoxylan with a xylose (in its main chain) and with an arabinose

polymer (in its side chain). To the presented patients BioBran/MGN-3 was given per oral in doses between 12 and 45mg/kg twice a week parallel to the optimized, lectin-oriented ME therapy.

WGE (trade name AvemarR) is a complex of multiple, biologically active molecules obtained from fermented wheat-germ extract. Its biological effects are related to 2-methoxy-p-benzoquinone (2-MBQ) and 2, 6-dimethoxy-p-benzoquinone (2, 6-DMBQ) in the form of glucoside. During the fermentation the quinones are released by the glucosidase enzyme of the yeast fungus. The 1045 mg tablets are manufactured and supplied by Biopharma Kft, Kunfehértó, Hungary. WGE is standardized for its 2, 6-DMBQ content (0.4 mg/g concentration on dry matter basis). In presented cases WGE was given per oral in doses between 50 and 80 mg/kg/die four times a week (on the day of immunotherapy and 24h thereafter).

Patients

Ethics committee:

Ethics committee proposed to observe and publish case reports of own patients treated by standardized plant extracts. These and previous case reports may stimulate an interest for other research groups according to the opinion of the ethics committee. All patients have given an informed consent to process and publish their dates. They were informed that plant extracts can be regarded as a complementary therapy and it cannot substitute for conventional oncologic treatments. The patients were regularly controlled in various oncologic centers and parallel they were also treated with plant immunomodulators and monitored in private praxis (in Switzerland and Hungary).

Eligibility criteria of patients with malignant tumors:

Inclusion criteria: 1. histological defined malignant tumor; 2. patients did not require nursing; 3. at begin of observation they did not receive morphine derivates; 4. measurable tumor parameters by CT scans or sonography.

Exclusion criteria: 1. no histological data; 2. Karnofsky index is less than 60; 3. undesired side effects (such as allergy).

Results and Discussion

Previous clinical observations were published in case reports [20-23] and we present them only in a short form and discuss together with new clinical data.

Clinical results with sarcoma patients published previously

As reported previously [20], six sarcoma patients show astonishing remission under optimized lectin-oriented doses of ME, partly in addition to other oncotherapies. A patient with lung metastases of liposarcoma was regularly given mistletoe therapy without other treatments. His clinical progress reveals that the optimized mistletoe dose alone was able to result in remission of metastases. Without lectin-oriented dose of ME the metastases of the lung recurred while as under a strict lectin oriented dose regression took place. Until today the patient has survived for 21 years with excellent quality of life. In another liposarcoma patient with inoperable metastases of peritoneum and of the lymph glands simultaneous chemotherapy and lectin-oriented ME-therapy brought about partial remission, solely under ME-therapy the remission has persisted for three years. As mentioned, preclinical data in the tumor model with xenotransplanted sarcoma [11] suggest that lectin-oriented ME therapy is capable of enhancing the efficacy of certain oncotherapies. Two patients with lung and peritoneal metastases of uterus stroma sarcoma were given lectin-oriented ME therapy in addition to hormone therapy (gonadotropin-releasing hormone analogue) or chemotherapy (epirubicin). In spite of the fact that the efficacy of hormone therapy on the recurrent low-grade stroma sarcoma is controversial its combination with ML resulted in a partial remission. In the second stroma sarcoma patient a complete remission already occurred after two chemotherapy cycles so that the planned sixth cycle could be abandoned. Two patients suffering from angiosarcoma were on the lectin-oriented ME therapy following operation. Both patients showed a complete remission and they have remained without relapse for three and four years now.

Clinical results with hepatic metastases published previously

As in another case reports were published [21], using standardized plant extracts (see table 1) the clinical progress of seven patients showed a complete or nearly complete remission of hepatic metastases. These results are therefore surprising since as it well known, that after a chemotherapy hepatic tumors rarely disappear completely and the duration of responses is short. Hepatic resection in many cases also results in no long-term benefit. In one case the complete remission of hepatic metastasis was reached by immunomodulator alone [22]. In a 72-year-old patient, tumor extirpation of a malignant melanoma (IA SSM Clark level II, pT1 N0 M0, Breslow 0.375 mm) from the right upper arm was carried out in 1992, and because of a second nodular melanoma (IIA, pT3 pN0 pM0) on the right shoulder a second surgery was performed in 1999. In August 2001 three axillary lymph nodes (right) were removed. At the same time in segments 4/5 a solitary hepatic metastasis was detected. From October 2001 the patient was given lectin-standardized ME therapy. In June 2002 a complete remission of liver metastasis was established. Until 2014 no recurrence of the liver metastasis and normal liver functions were regularly observed. The quality of life of patient has been excellent. The multiple liver metastases of two breast cancer patients showed a complete and a partial remission after a combined therapy of hormones (anti-estrogens: Femara as well as Letrosol) and immunomodulators during the observation period of 11 and 10 months. As it is well known, anti-estrogens are able to inhibit the proliferation of mammary cancer cells and therefore it can be speculated that the effect of anti-tumor immune cells on tumor progression is enhanced by this hormone therapy.

Similarly to anti-estrogens, cytostatic drugs with antiproliferative effects seem to be helpful for anti-tumor immunological mechanisms. Because the now 50-year-old patient had ductal mammary carcinoma [T2 N1 (3/17) Mx], a tumorectomy in January 2010, and subsequently a hormone treatment (Femara) and chemotherapy (six cycles epirubicin and docetaxel) were carried out. In April 2011 multiple hepatic metastases were detected in PET/CT. In December 2011 seven liver metastases were removed by surgery. Six weeks later a considerable progression of hepatic metastases was established in PET/CT. Because of the bad liver functions and bad quality of life only a mono-chemotherapy with reduced dose (2500 later 1500 mg Xeloda /day) was given. In the same time an immunomodulatory treatment with lectin-standardized ME, MGN-3/Biobran and WGE was started. In April 2012 a considerable remission of the hepatic metastases (only three small metastases) were detected in CT. The liver functions and tumor markers have been normalized. In August 2012 a nearly complete remission of the hepatic metastases could be

established. (The metastases were not measurable in CT). So far the quality of life has been excellent; the patient has been able to work 100% during an observation period of 11 months. These observations suggest the hypothesis that under certain circumstances these immunomodulatory treatments combined with low doses of chemotherapy may be more effective than their combination with high doses of cytostatic drugs.

Two case reports were also represented on patients whose hepatic metastases were removed by surgery [22]. These case reports supported the hypothesis that preoperative and postoperative treatments with these standardized immunomodulators may improve the prognosis of patients following a liver metastasis operation.

Two new case reports presented now in figure 1 and 2

In a now 70 year old patient (Figure 1) an adenocarcinoma of stomach with coeliac lymph node metastases (T3N1Mx) was in November 2010 established by gastroscopy, biopsy and computed tomography (CT) scan. From December 2011 until May 2012 six cycles Epirubicin (79 mg/m^2), Cisplatin (76 mg/ m^2) and Xeloda (1000 mg/ m^2) were given. After three cycles the question arose as to whether her gastric tumor is responsive to this chemotherapy or not. Therefore in February 2012 a CT scan investigation was carried out and no change was established. The next three cycles of the same chemotherapy were combined with standardized plant immunomodulators and thereafter in May 2012 CT scan investigation showed a nearly complete remission. In Juni 2012 was the rest of tumor chirurgical removed. Until April 2014 the patient received only immunomodulators without an oncologic treatment and CT scan investigations did not show any relapse of her diseases. Her body weight increased by more than 10 kg and her quality of life is excellent.

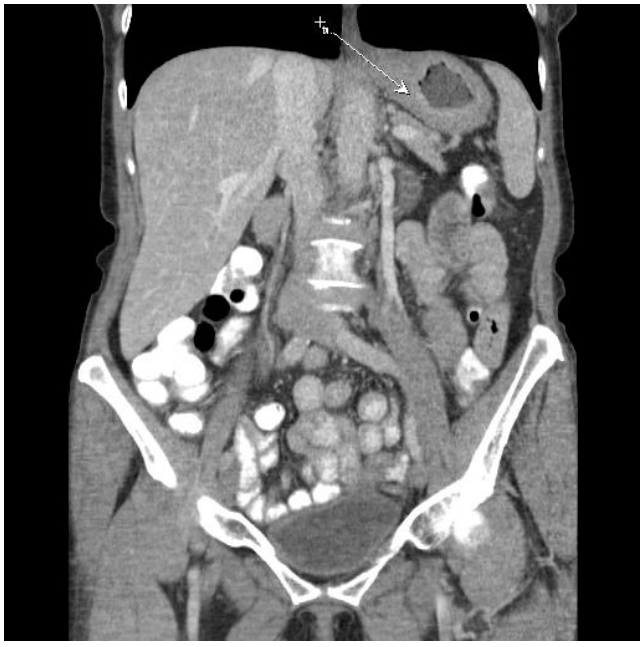

Figure 1a: Computed tomography (CT) scans of stomach cancer in a 70-year-old patient. She has received three cycles Epirubicin, Cisplatin and Xeloda and no change was established.

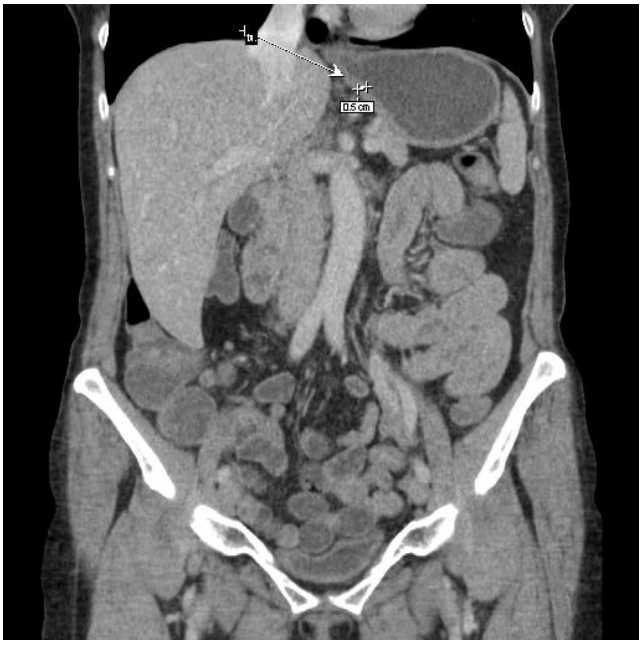

Figure 1b: Figure 1: The next three cycles chemotherapy were given in the same doses but combined with ME/ML, BioBran and WGE and after three months nearly complete remission was observed.

Another 65 years old patient (presented in figure 2) had a ductal mammary carcinoma [T2 N1 (2/14) M0], a tumorectomy was carried out in May 2003, and subsequently six cycles chemotherapy and irradiation (50GY) were adjuvant given. In June 2011 a lung metastasis was established in right segment 6 (S6) by PET/CT scan which was in July 2011 chirurgical removed by tumorectomy. In September 2012 a recidivation of lung metastasis in S6 was established by PET/CT scan. From Oktober 2012 low dose of Xeloda (2500mg/die) was applied and after four cycles the question arose as to whether her lung metastasis is responsive to this chemotherapy. Therefore a CT scan investigation was carried out in March 2013 which did not found any change. From March 2013 the same doses of Xeloda were combined with standardized plant immunomodulators and after the next four cycles in July 2013 a complete remission was established by PET/CT scan. The chemotherapy was stopped and only the immunomodulatory treatment was followed. The last PET/CT control in November 2013 did not find any relapse of her disease and her quality of life is excellent.

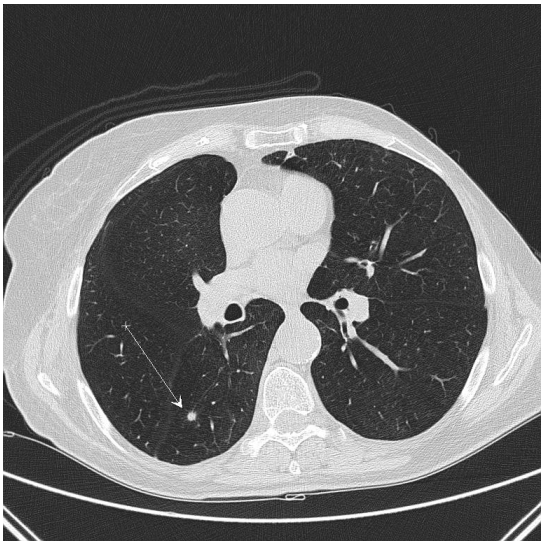

Figure 2a: Computed Tomography (CT) scans of lung metastasis of breast cancer in a 63-year-old patient. She has received five cycles Xeloda mono-chemotherapy and no change was established.

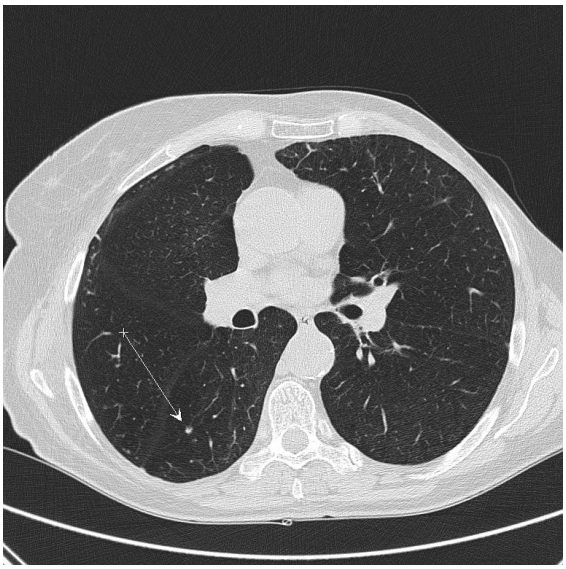

Figure 2b: The next four cycles of chemotherapy were given in the same doses but combined with ME/ML, BioBran and WGE. After four months nearly complete remission was observed, and the surgical operation was not necessary.

In the last two cases (illustrated on figure 1 and 2) the possibility cannot be ruled out that the remissions may be due to the time elapsed. Still, taking the previous clinical data into consideration these cases may also support the hypothesis that a combination of immune therapy with cytostatic drugs may be of additional benefit compared to a monotherapy with either substance. In addition, in second case report it is very improbable that low doses of Xeloda alone can induce a complete remission of lung metastasis suggesting a hypothesis that under certain circumstances these immunomodulatory treatments combined with low doses of chemotherapy may be more effective than their combination with high doses of cytostatic drugs.

Standardizes plant immunomodulators, such as ME/ML, MGN-3/BioBran and WGE have no toxic side effects

Standardized plant extracts described above have a great advantage; they don't cause any side effects. In terms of safety and toxicity of ME, available studies indicate that mistletoe therapy is well tolerated, and serious adverse events were not reported [23]. MGN-3/BioBran has also been judged to be a highly safe food supplement as it was verified by conducting acute oral toxicity, mutagenicity, subacute toxicity, and antigenicity studies [24]. WGE has been put on the market as a non-toxic dietary supplement. Toxicological studies with high doses of WGE (3g/kg) did not show any deviation from the controls [19].

Improvement of quality of life in tumor patients after an immunomodulatory treatment

Behavioral co-morbidities in cancer patients were often found to be associated with decreased activity of cellular innate immune responses and with an elevated activity of regulatory T cells [25]. The most often observed behavioral alterations of patients with cancer include fatigue, depression, pains and cognitive dysfunction [26]. Consequently, the influence of an immunomodulatory treatment on the cancer-related reduction of quality of life (QoL) attracts growing interest.

In a previous study [27] QoL was investigated in tumor patients who were treated with standardized plant immunomodulators. To monitor their QoL during this period, SF-36 questionnaires were regularly filled out at four months intervals. The score values of SF-36 questionnaires were regularly compared with untreated match pair control persons. The score values were evaluated 0, 4, 8, 1 2, 16, 20 and 24 months after the start of the observation period. Significant elevated differences in score values between patients and match pair control persons were found after 12, 16, 20 and 24 months. Particularly the tumor-related fatigue syndrome and pains were beneficially influenced. Consequently, it is suggested that the standardized plant immunomodulators can be helpful in the improvement of QoL of tumor patients.

The role of external factors in clinical progress of tumor patients treated with standardized plant immunomodulators

Since an equilibrium disturbance in psychic situation and the tumor-induced immunological dysfunctions appear to be strongly associated with each other, the role of placebo effects may be also involved in the improvement of patients treated with standardized plant immunomodulators. Since the most frequent behavioral alterations of patients with cancer such as fatigue and depression can show an upturn during the immunomodulatory treatment, the patients are beginning to think more positively which can be helpful in the conventional oncologic therapy.

Conclusion

Standardized plant extracts with PAMP-like activity may open new perspectives for oncologic therapy improving the tumor - related dysfunctions in innate immune system which can enhance the effectiveness of oncologic treatments and improve the quality of life. In

order to further substantiate these claims, more rigorous research is urgently needed.

Disclosure statement

The authors declare that there is no competing or other conflicting interest in relation to this paper. The sponsor had no influence on the design or conduct of the clinical reports, interpretation of data or approval of the manuscript.

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