Oral Colostrum Macrophage-activating Factor for Serious Infection and Chronic Fatigue Syndrome: Three Case Reports

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Abstract. *Background: Gc protein-derived macrophage-activating factor (GcMAF) immunotherapy has been steadily advancing over the last two decades. Oral colostrum macrophage-activating factor (MAF) produced from bovine colostrum has shown high macrophage phagocytic activity. GcMAF-based immunotherapy has a wide application for use in treating many diseases via macrophage activation or for use as supportive therapy. Results: Three case studies demonstrate that oral colostrum MAF can be used for serious infection and chronic fatigue syndrome (CFS) without adverse effects. Conclusion: We demonstrate that colostrum MAF shows promising clinical results in patients with infectious diseases and for symptoms of fatigue, which is common in many chronic diseases.*

Gc protein-derived macrophage-activating factor (GcMAF) has various functions, such as macrophage activation and anti-tumor activities (1, 2). In the GcMAF development timeline, there have been two major types of GcMAF until now: purified GcMAF and serum GcMAF (3). In 2014, Saisei Mirai developed a new form of macrophage-activating factor (MAF) made from colostrum in collaboration with the Tokushima University. This new form, referred to as colostrum MAF, is manufactured using bovine colostrum instead of human serum (4). It is administered orally in an acid-resistant enteric capsule to activate macrophages in the gut-associated lymphoid tissue (GALT) and as a powder in the mouth to activate macrophages in the lymphoid tissue of the mouth and throat, known as the Waldeyer's tonsillar ring or pharyngeal lymphoid ring. In addition to these two areas of the body, colostrum MAF may be administered in other areas where macrophages reside. In terms of practical clinical use, colostrum MAF has certain advantages over MAF produced from serum because it is derived from bovine colostrum, a food, instead of human serum, and it is administered orally and sub-lingually instead of injection. These factors favor their widespread use in the near future.

In recent years, immunotherapy has become an attractive new strategy not only in the treatment of cancer but also in the treatment of many other acute and chronic diseases. GcMAF-based immunotherapy has wide application for use in many diseases by activating macrophages to stimulate the immune system. The herein presented case studies suggest a new protocol for the treatment of infectious diseases and chronic fatigue syndrome (CFS) using food-based colostrum MAF.

Macrophages are phagocytic cells that are an important part of the innate immune system that increase in numbers in response to an infection. They recognize, engulf and destroy pathogens, cancer cells and foreign substances, release cytokines and are involved in the removal of cellular debris and clearing of cells that have undergone apoptosis (5). They provide a first-line of defense in protecting the host from infection. Macrophages broadly consist of two classes: tissue-resident macrophages and infiltrating macrophages. The majority of tissues in the body contain tissue-resident macrophage populations (6). Examples of tissue-resident macrophages include intestinal macrophages of the

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gastrointestinal tract, Langerhans cells and dermal macrophages of the skin, Kupffer cells and motile liver macrophages of the liver, brain microglia, alveolar and interstitial macrophages of the lungs, red pulp macrophages of the spleen and bone marrow macrophages. All these macrophages, by definition, reside in their respective tissues and perform homeostatic tissue-specific functions (6-8). Inflammatory monocytes, the source of infiltrating macrophages, selectively travel to the sites of inflammation, produce inflammatory cytokines and contribute to local and systemic inflammation (9). Infiltrating macrophages are found in pathological settings, such as cancer, atherosclerosis and metabolic diseases. (8). Macrophages also play an important role in wound healing, as well as skin repair, contributing to activation of skin epithelial stem cells and the cyclic activation of adult hair follicle stem cells. This finding may have translational implications for skin repair, hair re-growth and inflammatory skin diseases (10).

The mucosa-associated lymphoid tissue (MALT) is scattered along mucosal surfaces in our body and makes up the majority of the human lymphoid tissue. The main function of MALT is to produce and secrete immunoglobulin A (IgA) (11, 12). MALT is populated by lymphocytes, such as T-cells and B-cells, as well as macrophages and plasma cells, where each cell is well-situated and prepared for encountering antigens and pathogens passing through the mucosal epithelium. The components of MALT are sub-divided into several groups, such as gut-associated lymphoid tissue (GALT) and Waldeyer's tonsillar ring or nasal-associated lymphoid tissue (NALT), which is made up of the palatine tonsils, nasopharyngeal tonsil (adenoid), lingual tonsil and the less prominent tubal tonsils. Because the tonsils are the first site of contact with inhaled and ingested microorganisms, they are considered the first-line of defense against exogenous invaders (13). GALT is considered the largest macrophage pool in the body playing a very important role in maintaining and regulating mucosal immunity (11, 12). Oral colostrum MAF is directly aiming at activating the huge number of macrophages in these parts of the body to stimulate the immune system.

The general goals of GcMAF and oral colostrum MAF immunotherapy are to improve well-being and quality of life (QOL), return the patient to good health so that they are able to participate in regular life-style activities, achieve long-term survival, enhance the effect of other therapies, repair the immune system, increase the number of monocytes and activate them to destroy cancer cells, viruses, bacteria and other pathogens in the body and, finally, increase the rate of maturation of dendritic cells (3).

Infection in cancer patients has been widely reported suggesting that various factors, either disease-related or therapy-induced, render cancer patients more susceptible to infections compared to otherwise healthy people (14). In terminal-cancer patients, infection can quickly become a life-threatening risk without effective treatment options. Moreover, infection is responsible for significant patient distress and adverse symptoms, further reducing quality of life of patients (14).

Chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is a devastating and complex disorder with uncertain cause (15). People with CFS have overwhelming fatigue and a number of other symptoms that do not improve by bed rest and tend to get worse after physical activity or mental exertion. They often function at a much lower level of activity than they were capable of before they became ill. The primary symptoms of CFS is unexplained severe fatigue lasting at least 6 months that is not improved by bed rest (16, 18). Defining symptoms of CFS include post-exertion malaise lasting more than 24 hours, unrefreshing sleep, impaired memory or concentration, muscle pain, pain in the joints without swelling or redness, headaches, tender lymph nodes in the neck or armpit and a sore throat that is frequent or recurring (17). Many CFS patients may also experience other symptoms, such as irritable bowel syndrome, depression or other psychological problems, chills and night sweats, visual disturbances, brain fog, dizziness, problems with balance and sensitivities to foods, odors, chemicals, medications or noise (17, 19). Because there are no blood tests, scans or other laboratory tests to diagnose CFS, diagnosis is usually made by ruling out other possible diseases. As there are no prescription drugs developed specifically for CFS, it is generally considered as an incurable disease. Doctors treating CFS tend to treat each of the symptoms individually with a wide range of drugs without much success.

The cause of CFS has as yet not been identified; however, infections and immune dysfunction are thought to play a critical role in the development of the disease. In addition, numerous viruses, such as Epstein-Barr virus (EBV), human herpesvirus-6 (HHV-6), HHV-7 and HHV-8, herpes simplex virus type 1 (HSV-1), HSV-2, measles virus, adenovirus type 2, Enterovirus and human cytomegalovirus (HCMV), have been implicated in subsets of patients. However, results have been mixed and inconclusive (15, 19). Chlamydia has been also found in subsets of patients. In particular, studies have found widespread evidence of Mycoplasma species infections in CFS patients, a finding extensively reported in the scientific literature (16, 18). It has also been suggested that enterobacteria are involved in the etiology of CFS. Maes *et al*. (20) report elevated serum levels of IgA and IgM against the LPS of Gram-negative enterobacteria in CFS patients indicating increased gut permeability and an anti-LPS immune response with subsequent gut-derived inflammation causing systemic inflammation and oxidative and nitrosative stress, thus pointing to a new pathway in CFS (21). This kind of chronic immune activation has been long thought to be a component of CFS (17) and studies in CFS

patients have identified a number of pro-inflammatory cytokines, to be correlated with the disease. For example, LPS-induced cytokine levels were strongly correlated with general fatigue levels in CFS patients (22). Interleukin (IL)-6 has been shown to induce fatigue symptoms in healthy subjects and CFS patients (22). Therefore, identifying infections in these patients is of prime importance (18).

Aside from CFS, fatigue is one of the most commonly reported symptoms in cancer patients that can be extremely debilitating and may have a severe negative impact on quality of life (23). Even cancer survivors, and those of other life-threatening illnesses, report chronic fatigue lasting months to years after completion of treatment. Despite the high prevalence of fatigue, little is known about its pathogenesis.

Overall, it is reported that this symptom is a problem in 75 to 90 percent of patients with cancer or other chronic illnesses (24).

Results

Case Report 1. A 74-year-old female with pancreatic cancer, multiple liver metastasis and rheumatoid arthritis was admitted to hospice for terminal care. On October 4th, 2014, while in the hospice, she developed high fever for which she was treated, unsuccessfully, with antibiotics. She lost consciousness on October 8th, 2014 and, two days later, she was temporarily transferred to another hospital for emergency tests and treatments. No evidence of pneumonia was found and, thus, on October 14th, 2014, she returned to hospice and received intravenous hyperalimentation (IVH) feeding. The patient remained in deep coma with continuing high fever and antibiotics not working, but causing renal function disorder. On October 18th, 2014, she was diagnosed to have several hours to several days to live, so family members gathered to farewell her in the hospice. On that night, the patient's son began to apply colostrum MAF powder dissolved in a small amount of water to the lymphoid tissue areas in the mouth, 2 times per day. The next day the patient showed a reduction in the fever and, in 3 days, the fever had almost disappeared. On October 29th, 2014, after 3 weeks in coma, and 11 days after starting oral colostrum MAF, the patient opened her eyes and was able to follow movements with her eyes. On November 4th, 2014, the patient started to talk and wanted to eat, being surprised the month was already November. At this point, eating rehabilitation started, while, at the same time, continuing IVH. The doctor in the hospice said that this result was a miracle. It was the first case observed out of 2,000 patients who died in the same situation, thus rendering oral colostrum MAF an amazing medicine.

Case Report 2. A 71-year-old female with CFS and suffering from symptoms, such as dizziness, chronic fatigue, palpitation, tachycardia, depression, unrefreshing sleep, stomach pain, regular sore throats and other disturbances for around 40 years. She was diagnosed, by physicians and psychotherapists, with autonomic neuropathy, climacteric disorder, depressive state, Meniere's disease, chronic gastritis, cardiac neurosis, chronic cystitis, post hepatitis B infection and colon polyps. Her blood tests showed no abnormality except cholesterol, which was slightly elevated, with sometimes borderline elevated transaminase levels. Brain magnetic resonance imaging (MRI) scan, cardiac catheter examination and gastroscopy showed no abnormality within the last 2 years. Colonoscopy showed colon polyps, which were removed during the colonoscopy examination and an abdominal computed tomography (CT) scan showed only a liver cyst. On November 5th, 2014, she started taking daily colostrum MAF powder in the mouth, exposing the lymphoid tissue with the resident macrophages and, also, colostrum MAF orally in an acid-resistant enteric coated capsule. Within a few days, she noticed that her malaise, dizziness, tachycardia, insomnia, nocturnal urination and stomach pain were improving and she was feeling better with improved quality of life. Over an one-month period, she also noticed that her skin became smooth and silky and that the blotches on her face and arms became lighter, disappearing in some places on the skin. She was very happy, being able to do her usual work with more energy like most other people do. Over a four-month period, she also noticed improvements in hair growth on her head.

Case Report 3. This last report concerns a 45-year-old female with CFS. She is the daughter of the previous case-report patient. She had stomach pain, severe fatigue, especially after work, unrefreshing sleep, headaches, pain in the joints and other disturbances since she was 20 years old. When she was younger, her body weight was 43 kg, which declined over the years to 37-38 kg. Her fatigue could not improve by bed rest or taking medications and became worse with work. Her blood tests showed no abnormality and a brain MRI scan, abdominal MRI scan and an ultrasound scan were also normal. Gastroscopy showed gastritis and the presence of *H. pylori* bacteria in her stomach for which she was treated with antibiotics. After getting rid of the bacteria, her severe stomach pain continued and she was not able to control the symptoms even with proton pump inhibitors (PPIs). On November 12th, she started taking colostrum MAF powder in the mouth and one capsule orally/day, as described in the previous case report. In a couple of days, she felt much better with reduced malaise in the morning and reduced stomach pain. She was able to move her body easily without the usual joint pain, muscle pain and fatigue and began forgetting to take her stomach pills. Within an one-month period, she noticed that the freckles on her face became lighter and her skin became smooth and silky. She was very happy because she did not have symptoms of

malaise anymore, had good sleep, significantly decreased stomach pain and decreased menstrual cramps. Within a 4-month period, she noticed her hair was re-growing all over her head. Due to occupational use of paint thinner, she had lost hair on her forehead, which was now coming back.

Discussion

At some point, patients with a terminal illness tend to be placed in palliative care, which provides pain relief and other measures designed to make the end-stages of terminal illness as comfortable as possible (14). It is common that, once a patient reaches this point, curative treatment efforts are discontinued or scaled back. By this stage, the treatment for the disease may no longer be effective and can be as painful and uncomfortable as the disease itself. Thus, naturally, the focus turns from treatment to palliation with one of the most important goals of medical practitioners being to ease suffering and improve quality of life (14). With this new goal in mind, we need to consider the factors that cause discomfort and reduce quality of life. In patients with cancer, fatigue and anorexia rank as the top two reasons for emotional and physical distress, with pain ranked third. Nausea, constipation, altered mental state, such as delirium, and dyspnea have been described as the next most common symptoms. It is not uncommon for family members to interpret fatigue as means that the patient is "giving up" when, actually, the symptom of fatigue is beyond the patient's control (24).

Infection is responsible for substantial patient distress and an important contributing factor in many of these adverse symptoms (14). Mohammed *et al*. (14) take it one step further to suggest that, although infection in cancer patients has been widely reported, very few studies have focused on infection and its management in palliative care patients. In palliative care, antibiotic use is common practice in patients with advanced cancer as one of the supportive treatments near the end of life as a means of controlling infections (14). A big dilemma for physicians caring for terminal cancer patients is deciding whether antibiotics are effective and able to provide benefit or not. Also, it must be considered that antibiotics are not necessarily safe, have a long list of potential adverse effects and increase the risk of anti-microbial resistance. In terms of colostrum MAF, this dilemma is being waived since there are no side-effects and no risk of resistance to treatment. Therefore, the benefit-risk ratio is very high with this option. By comparison, the benefit-risk ratio of antibiotics is more difficult to determine. As indicated in our case study of infection in a terminally-ill cancer patient, GcMAF-based immunotherapy was proven quite effective as it could play a critical role in combination with, or even without, antibiotics in patients with cancer and infections. The treatment with colostrum MAF has been shown to be non-toxic, improving quality of life (QOL), prolonging life and curing the infection, which addresses the major goals of palliative care.

Concerning CFS, we highlighted case reports of two patients with CFS who had very good effects from oral colostrum MAF. It is suggested that oral colostrum MAF can be used to achieve much better outcomes for patients with CFS, including additional benefits, such as skin repair, decreased freckles, blotches and hair re-growth. Even though the cause of CFS has as yet not been identified, research suggests that infections and immune dysfunction are thought to play a critical role in the development of the disease. Key findings point to increased gut permeability and an anti-LPS immune response to Gram-negative enterobacteria with subsequent gut-derived inflammation that cause systemic inflammation and oxidative, as well as nitrosative stress. Research by our group has reported that macrophage activation with GcMAF-based immunotherapy, unlike that of LPS, does not result in nitric oxide (NO) and tumor necrosis factor (TNF)-α and IL-1β cytokine production (4, 25). According to research by Uto *et al*. (4), 10 ng colostrum MAF has a significantly higher macrophage phagocytic activity than 1 μg LPS. Therefore, it is suggested that macrophages have a much higher affinity for activation by GcMAF than LPS. Administering exogenous GcMAF will result in suppression of the LPS-related macrophage activation and, thus, GcMAF will induce a good phagocytosis without IL-1β and TNF-α release. These experimental results are interesting and correlated with our clinical findings of reduced fatigue in CFS patients with colostrum MAF therapy considering the findings that a number of cytokines are implicated in fatigue symptoms.

There are two possible ways colostrum MAF acts. Oral administration of the enteric capsule allows colostrum MAF to reach the gut where it can activate macrophages in the Payer's patches and, from there, enter the blood stream. There is also the possibility that colostrum MAF can act *via* sub-lingual absorption into the bloodstream where it can reach many places in the body. Our clinical results suggest the possibility that the colostrum MAF molecule can be absorbed *via* either of these routes allowing it to have similar effects to injected GcMAF.

Some researchers suggest that symptoms of CFS and fatigue in patients can be caused, generally, by chronic cytokine production due to bacteria when macrophages are activated by LPS. Our work and that of others show that macrophage activation by purified GcMAF, serum GcMAF and colostrum MAF does not result in production of cytokines, while it still increases phagocytosis (4).

In conclusion, it is clear that infectious diseases are important factors in both chronic fatigue syndrome and cancer, with both diseases sharing the common symptom of fatigue. Considering our case studies of a terminal cancer

patient with serious infection and patients with CFS, it is clear that oral colostrum MAF addresses the possible cause(s), as well as the symptoms of fatigue in these very different and seemingly unrelated diseases. We propose further clinical and experimental work to elucidate the mechanisms by which MAF has beneficial effects on fatigue in cancer, CFS and other chronic diseases. Importantly, colostrum MAF shows promising clinical results in patients with infectious diseases and for symptoms of fatigue, which is common in many chronic diseases.

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