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Individualizing medical treatment in chronic fatigue syndrome/myalgic encephalomyelitis: Evidence for effective medications and possible relevance to “Long-Hauler Syndrome” in Covid-19 affected patients

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Abstract

Large controlled studies of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) have shown no effective medical treatment for this disorder. There are individual patients, however, with dramatic responses to some medications. We report two patients with clear responses to rintatolimid and galantamine characterized by rapid reduction of symptoms on starting treatment and return of symptoms on withdrawal. As in cancer, CFS/ME is a heterogeneous disorder but unlike most cancers, such as melanoma, breast cancer, and B-cell lymphoma, CFS/ME has no known biological marker that can distinguish between subtypes. We suggest an approach to medical treatment of CFS/ME that could be utilized by primary caregivers that offer the possibility of more rapid and complete recovery from this debilitating disorder. Current studies indicate that prolonged symptomatic recovery from infection with Covid-19 (“long hauler syndrome” or PASC, for post-acute sequelae of Covid-19) represents a severe form of CFS/ME and thus may also be amenable to personalized medicine with specific medications.

Keywords: chronic fatigue syndrome; myalgic encephalomyelitis; treatment; rintatolimid; galantamine; Covid-19.

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Introduction

Chronic fatigue syndrome (CFS) is a well-known but poorly understood disorder characterized primarily by severe prolonged disabled fatigue, cognitive dysfunction, and sleep abnormality with the diagnosis requiring an extensive evaluation to rule out any disease that could be responsible for the symptoms [1]. Also known as myalgic encephalomyelitis (ME) [2] or systemic exertion intolerance disease (SEID) [3], CFS is recognized as an often severe debilitating illness [4] which can be triggered by a number of infectious agents including EBV, HHV-6, and giardiasis [5-7] and probably represents an overlap with the “long hauler syndrome” seen in people infected by Covid 19 [8]. There can also be non-infectious triggers such as physical or emotional stress including acute trauma [9], may also be an autoimmunity predisposition [9-11], and immunologic abnormalities, such as decreased natural killer cells, have been shown in patients [9] and asymptomatic family members [11]. Research shows impaired HPA axis activation, hypocortisolemia [12], and decreased DHEA and DHEA-S levels [13] are significantly associated with CFS. The death rate is at least 3 times more frequent in females [14] perhaps related in part to the higher frequency of autoimmune disease in women. No specific test is currently available to diagnose the condition; diagnosis is solely based on clinical presentation and after excluding other medical conditions.

An editorial in the *Annals of Internal Medicine* [4] reviewing the importance of ME/CFS as a “real illness” noted that a systematic review of treatment by the Agency for Healthcare Research and Quality (AHRQ) for a workshop organized by the National Institutes of Health showed that some patients were helped by graded exercise and cognitive behavior, but added that “no drug treatments are of proven value, and that some treatments-particularly corticosteroids and galantamine-cause important adverse events”. Our experience with individual patients, however, strongly suggest the efficacy of galantamine and rintatolimod (Ampligen) in certain patients, and rather than discouraging research on these and other medications, we describe two patients, with apparently dramatic improvement in response to these different medications with different mechanisms of action, responses that were apparently not seen in the majority of CFS patients in clinical trials in the hope of encouraging more exploration into the use of various markers to identify specific therapeutic agents for specific patients. This issue is currently particularly important because of the increasing prevalence of “long-hauler disease” in patients getting Covid-19 infection [8, 15], quite possibly a severe manifestation of CFS and amenable to the same treatment.

Case report 1 (Rintatolimod)

This 49-year-old college professor and mother of two with a Ph.D. in history had been in excellent health until the fall of 1990 when she experienced an episode diagnosed as “Epstein-Barr”. Before then, she worked out regularly, had an active research agenda, an hour-long commute to work, raised a family, and participated in 4-5 conferences a year at various universities around the country. In the spring of 1991, she suffered from chronic bouts of bronchitis throughout her teaching semester. When not teaching, she describes herself as being “generally

pretty healthy.” Hoping to alleviate her problems, she had surgery to repair her deviated septum, but the procedure did not help.

Her health problems reached a more serious level when in October of 1994, she collapsed in her office at Villanova. From that point on, she was severely disabled and her health status continued to deteriorate. Although she still attempted to drive in 1995, she finally quit after realizing she was “on a curb near the local post office and had no idea how [she] got there.” This once active woman walked with a cane in 1995, but by 1998 she could not go anywhere without a wheelchair.

Before this patient began taking rintatolimod (Ampligen), she was told she had “leukocytes riddled with HHV-6a,” and a positive test for 37kDa RnaseL, an endoribonuclease associated with immune dysregulation that was reported in CFS patients but not in healthy controls [16]. She was prescribed a number of medications to alleviate symptoms apparently caused by CFS, including Cytomel, Zoloft, Ultram, Florinef, Klonopin, Doxepin, Ritalin, and supplemental vitamins. Her condition continued to cause her enough discomfort that her house was outfitted with a raised toilet seat and rails and a shower bench with rails.

During this time, she also experienced more diverse symptoms. She had muscle weakness and problems with muscle control, a loss of balance, migraine headaches, and sensitivity to light and loud noises. She could not complete a 3-minute treadmill test, shuffled with a cane, and used a wheelchair when outdoors. Her weakness required her to be pushed in the wheelchair by others. Her cognitive impairment increased during this time as well. She suffered a loss of short-term memory, dyslexia, poor attention span, and severe central auditory processing difficulties. The mental confusion she experienced was similar to Alzheimer’s disease in that she would pour coffee into the silverware drawer unaware that it was not a cup.

In the summer of 2018, she was started on intravenous Ampligen titrated up to a maximum dose of 400 mg/ 2x a week in an open trial. After six months on Ampligen, testing showed the 37kDa and HHV-6a were no longer detectable and her cognitive dysfunction had completely disappeared, although mental exertion was still exhausting. She no longer required the use of a wheelchair, which enabled her to start driving again but because she could only walk normally for short distances she was in need of a handicapped parking tag. She was also able to sleep during the day without her medications but still needed them at night.

The patient has taken Ampligen intermittently for more than 30 years and has followed a consistent pattern of improvement on Ampligen and relapse when off. The differences have been dramatic in exercise tolerance and cognitive function among other things. She can be in a wheelchair when off Ampligen for a period of time and after resuming the medication she is able to walk at least two miles. She is unable to read when off Ampligen but as a researcher, she has been able to publish papers when taking the medication. Over the last 30 years, she has not been able to have the same effect as in the beginning when improvement was immediate. Whether the gradual change is due to increasing resistance to treatment or the fact that she

is now 70 and three years older than when first starting Ampligen is uncertain. As of May 2021, the problem with Ampligen is financial. She has to pay \$40,000 a year for treatment which apparently is effective but difficult to afford.

Case Report 2 (Galantamine)

This 23-year-old college student dated the onset of her symptoms to the summer of 1996 when she went to Europe for an art history program but from the day she arrived, she found herself unable to establish a normal sleep pattern. She would awaken early every day, perhaps getting four hours of sleep, which became associated with increased forgetfulness and inability to study. She could not even remember the places she had seen and found that she had trouble keeping up with friends. When she returned to the U.S. her forgetfulness and decreased attention span became even more pronounced but despite or because of her cognitive difficulties she started swimming laps and then returned to long-distance running to prepare for an internship with professional athletes. The first week of the internship she found she could not even type one sentence and her main preoccupation was hiding her disability.

She returned to school, continued to have difficulty sleeping, and used the extra waking time to train for lacrosse. She spent 12 hours a day at a training facility plus taking a second job. By June of 1997, she had developed severe muscle aches, a constant sore throat, a new severe headache, and a speech disorder. Her cognitive dysfunction severely affected many activities and she became fearful of driving as she could not comprehend the meaning of red and green traffic lights. She decided that as long as she felt "brain dead" she would run more than 10 miles whenever she had a window of energy.

She was unable to function at school, sought medical help, and was given Prozac for depression although she did not feel depressed. The Prozac had no effect. In late October, when she was no longer willing to drive her car, she obtained medical leave. She was seen by one of us (P.H.L) who thought she clearly fit the criteria for CFS and the diagnosis was confirmed by another internist in Washington with considerable experience with this disorder. The patient returned to her parents' house where she was unable to walk on her own and sitting upright on the couch required her parents to prop her up. She noted in subsequent correspondence, now having recovered her normal cognition, "that I was 21 and my parents were washing my face and helping me to brush my teeth was disconcerting, but I was more of an observer at that point, too tired to be upset. Myalgia was perhaps the worst. I could not hold a cup with my hands. My father would sit on my legs and apply pressure to allay the pain." Her cognition at this time had been severely impaired and while she tried to keep a journal it was obvious that she had difficulty putting a legible sentence together.

She saw a psychiatrist in New York who tried Lithium and Effexor in early 1998 with only side effects as a result. She tried to attend a local school but could not concentrate and had given up hope of recovery when she was informed in January 1998 about a clinical trial of galantamine, a cholinesterase inhibitor apparently successful in delaying deterioration in Alzheimer's disease patients [17,18] and then being used in a clinical trial for CFS [19].

She was started on the galantamine trial in New York and after about four weeks on the medication, she notes that "I was driving, reading and conversing with a mental acuity that had

eluded me since 1996. I still had to regain muscle strength and fitness, but I was more active and energetic". She did not know if she was receiving the medication or a placebo but because she had GI side effects she assumed she was receiving galantamine. Throughout the study, she said that "the most obvious change in energy was that I was not 'paying for' being active....I began to slowly regain physical fitness and I read any book I could get my hands on...." She had one short relapse in March but then she could cook, clean, and spend time with friends whenever she wanted to. The first part of the study ended and she was off drugs for a month before restarting in the open trial. But before the start of the open trial, she had started losing her concentration and endurance again and had to quit her job. But by the time classes started in September, she felt that the drug taken on the open trial was having an effect and she was confident of her abilities. Her pills were taken away on October 7 and by the time she was able to get the medication from Switzerland on Oct 22 she was already feeling "tired and flaky." She started back-packing and wrote up her experience for a class on cognition in a neuropsychiatry program. She was able to discontinue the galantamine within a year after she had entered the first blinded clinical trial and returned to school where she graduated. She has been able to maintain an active life crediting her continued well-being to a healthy diet and knowing her limitations.

Discussion

The current message that is generally accepted in much of the scientific community is that cognitive-behavioral therapy and graded exercise are the pillars of rehabilitation for patients with chronic fatigue syndrome and that clinical trials have not shown the effectiveness of any single agent [4,20], although one review suggests that some treatments such a psychiatric drug and steroids may help [21]. What has become apparent in many areas of medicine is that personalized medicine has become increasingly important as specific treatments can be found that are extremely effective in specific patients whose tumors show markers that can be targeted effectively by specific agents. A well-known example is in breast cancer, where patients that have estrogen or Her2-neu receptors on their tumors have significantly better survival after treatment with hormone antagonists or Herceptin respectively.

CFS/ME is a greater challenge than breast cancer or other malignancies because while all of these diseases are heterogeneous, malignancies have specific receptors on cells that can be targeted with appropriate treatments whereas CFS has not shown any marker that is clearly a target for a specific treatment. Thus far, treatments that were reported to be effective in early trials of drugs like rintatolimod [22,23] and galantamine [24] have not been accepted as being generally useful [4,20].

It is apparent that the two patients reported here are not unique. Rintatolimod (Ampligen) has shown some effect in clinical trials of CFS/ME beginning with a double-blind placebo-controlled study of 92 patients and controls in four centers reported in 1994 [22]. This study used the Karnofsky Performance Score (KPS) and showed significant improvement in the scores of treated patients compared to controls. The KPS scores were accompanied by improvement in activities of daily living (ADL). A subsequent randomized trial of 234 patients at four sites [23] used improvement on an exercise tolerance (ET) test as the primary end point to study the effect of rintatolimod. KPS, ADL, and Vitality Score were secondary endpoints. A sig-

nificant improvement in ET was observed as well as a reduction in CFS/ME-related medication usage and improvement in the secondary endpoints as well.

Another study of 208 treated patients and approximately 50 placebo controls [25] used a modified Bruce ET test as a primary endpoint because many of the patients couldn't complete the previously used standard ET test. KPS and Vitality were secondary endpoints. In an analysis of the various studies completed by 2016 [26], Mitchell suggested that approximately 30-40% of treated CFS patients had some benefit from treatment with rintatolimod. A subsequent analysis [27] showed that 75 patients with duration of symptoms 2-8 years had improvement in ET more than twice that of the entire group of 208 treated patients. The other 133 patients (those with <2 years duration of symptoms or more than >8 years) had no significant response compared to the placebo group.

For galantamine, which now has gained wide acceptance in Alzheimer's disease [17,18], even in the large clinical trial of CFS which had 352 treated patients vs. 82 controls receiving matched placebo tablets that showed no statistically significant effect [19], there were individual cases with dramatic clinical responses that were accompanied by evidence of improvements by SPECT scan (Blacker, personal communication). In addition, an earlier open study of consecutively referred patients [19] included just over 20 who received pre-and post-treatment SPECT scans. Significant hypoperfusion was seen in over half the cases; in 6 cases the hypoperfusion completely reversed coincident with a robust clinical response to galantamine which was evident within a week.

The earlier study of 49 CFS patients by Snorrason et al.[24] reported 50-70% of treated patients noted improvement in fatigue, myalgia, and sleep compared to 10% of the placebo controls. In this study, the peak effect of galantamine was seen after 4-8 weeks. The major side effect in both studies of galantamine was nausea.

The need for identifying particular medications of potential therapeutic value in specific CFS/ME patients is a major medical issue. The prevalence of CFS/ME was reported by Jason et al as 422/100,000 [28] but they noted other estimates by Reeves at CDC of 238/100,000 and Wessley in the United Kingdom of 2600/100,000, these differences possibly due to the differences in populations studied as well as methodology. For example, Reeves' data came from a largely White population in Wichita while Jason's group studied an urban population with Latinos and African Americans. In addition to this large number of affected patients described with CFS/ME, it may well be relevant to add the number of Covid long-haulers since there are indications that they may have the same disorder as CFS/ME [8,15].

Regarding prognosis, the data from Shepherd and Chaudhari [29] indicate that the course of Patient 1 follows the majority of CFS patients but for Patient 1 the relapses and remissions are tied more to the use and discontinuation of Ampligen than the other intercurrent problems such as infections, operations, and stressful events cited by Shepherd and Chaudhari. Patient 2 is in the small group with sustained remissions which makes her response more persuasive as to the effectiveness of galantamine.

The reports to date suggest that exercise tolerance tests indicate which patients are likely to respond to rintatolimod while galantamine could act primarily on the cognitive disorder, but since individual patients could respond differently to person-

alized medicine, a physician in practice could consider a short clinical trial of one of the medications noted above, similar to the general recommendation to physicians that it is appropriate to try antibiotics for two weeks to distinguish between mastitis and inflammatory breast cancer before doing a biopsy (which could exacerbate the mastitis) [30,31]. As with the short 2 week trial of antibiotics in a woman with breast redness due to mastitis or inflammatory breast cancer, with rintatolimod and galantamine if the medication will have an important effect the subjective improvement is considerable within 2-4 weeks and therefore long trials should not be necessary. Another consideration for the therapeutic trial could be cost. Of the two medications discussed here, rintatolimod is clearly the more expensive and the more difficult to obtain. Galantamine is advertised for \$30.75 for 60 4 mg tablets at one supermarket with a special discount coupon and retails for \$153.33 (goodrx.com/galantamine?gelid=...). The effect on our patient was almost immediate. In the blinded trial, she was on 2.5 mg three times a day, whether the galantamine or a placebo (her gastrointestinal side effects suggested to her she was on galantamine). The trial doses ranged from 2.5 mg three times daily to 10 mg three times daily. The difference in response rate between the treatment and control group using the Clinician Global Impression Scores were highest with the 2.5 mg and 7.5 mg groups peaking at 12 weeks at 12% which was less than the prespecified level for clinical significance (25%) [19].

Conclusion

In conclusion, despite the failure of large controlled studies to be accepted by all members of the scientific community [4,20], these case reports support the claims of the authors of the relevant studies including large controlled trials [19,23-25] that specific medications may have a reasonably rapid and long term effect on an otherwise prolonged and disabling illness. CFS/ME is not rare and the current focus on long-hauler effects of Covid-19 infection, probably another manifestation of CFS/ME, adds to the need of those treating patients with these issues becoming aware of reasonable pharmaceutical approaches to their treatment.

Declarations

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