



Megestrol Acetate in the Treatment of Post COVID-19 Fatigue in a Patient of Advanced Cancer: A Case Report and Mini Review of Literature

Chaitanya R Patil¹ Nilesh A Dhamne² Prasad K Tanawade³ Namrata B Mestri⁴

¹Department of Pain and Palliative care, Kolhapur Cancer Center, Kolhapur, Maharashtra, India

²Department of Medical Oncology, Kolhapur Cancer Center, Kolhapur, Maharashtra, India

³Department of Radiation Oncology, Kolhapur Cancer Center, Kolhapur, Maharashtra, India

⁴Department of Pathology, DY Patil Medical College, Kolhapur, Maharashtra, India

Address for correspondence Chaitanya Patil, MBBS, MD, PDF, Department of Pain and Palliative care, Kolhapur Cancer center, Kolhapur 416005, Maharashtra, India (e-mail: docterchaitanya@gmail.com).

Ind J Med Paediatr Oncol 2022;43:139–143.

Abstract

Megestrol acetate is one of the pharmacological agents used for cancer-associated fatigue. To date, there are no studies on its use in the treatment of post-COVID-19 (coronavirus disease 2019) fatigue. So, we report a case of metastatic carcinoma lung with a partial response with three cycles of palliative chemotherapy. He was contracted with mild COVID-19 infection post three cycles of his chemotherapy. Post this episode, fatigue was his main and most troublesome symptom. After a thorough clinical history, physical examination, and investigations, type 2 post-COVID-19 syndrome was diagnosed. After explaining the risks and benefits, we started the patient on low-dose megestrol acetate (160 mg/d per oral) with low to moderate benefits. However, upon increasing the dose to 480 mg/d, the benefit on the subjective quality of life was significant. Studies with a larger sample and randomized controlled trials have to be conducted to substantiate the hypothesis and actual effect of megestrol acetate in the treatment of post-COVID-19 fatigue.

Keywords

- ▶ post COVID-19 syndrome
- ▶ advanced cancer
- ▶ fatigue
- ▶ megestrol acetate

Introduction

Cancer patients describe fatigue as exhaustion and a decrease in energy and enthusiasm in routine activities.^{1,2} It is an overlooked symptom that has a negative impact on the quality of life of the patients.^{3–5} Studies report that fatigue is a persistent symptom after infection with COVID-19.^{6–8} The multiple mechanisms explained for fatigue in both scenarios are changes in neurotransmitter levels, inflammation, psycho-

logical disorders, stress levels, cognitive dysfunction, and substrate metabolism. The mechanism involving inflammatory mediators is of paramount importance in the present context.⁸ This inflammatory cytokine-related primary fatigue has central and peripheral effects. Central effects are changes in the hypothalamic-pituitary-adrenal axis and neuronal system. Altered muscular metabolism leading to energy imbalance constitutes the peripheral effect.⁸ Medical research continues to find many possibilities in the pathophysiology

published online
April 14, 2022

DOI <https://doi.org/10.1055/s-0042-1742616>.
ISSN 0971-5851.

© 2022. Indian Society of Medical and Paediatric Oncology. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of fatigue, but the answer remains elusive. Megestrol acetate is one of the pharmacological agents postulated to reduce fatigue in an oncological background.^{9,10} With this background, we report a case of post COVID-19 fatigue in an advanced case of cancer treated with megestrol acetate.

Case Report

The present case is a 56-year-old moderately built male with metastatic lung carcinoma attending the palliative care department for symptom control. Upon assessing the Edmonton symptom assessment scale revised (ESAS-r) (→ **Annexure 1**),¹¹ the patient reported symptoms such as fatigue, mid scapular pain, nausea, anorexia, and constipation. He scored his pain in the mid-scapular region to be 2/10, anorexia to be 3/10, and fatigue to be 7/10. Fatigue was generalized and increased after doing routine activities. Fatigue had started when he contracted the COVID-19 infection, and after treatment, it persisted. The pain in the mid-scapular region was a dull aching type. The onset of pain was gradual and progressive in the last 3 weeks. The pain did not interfere with the sleep cycle of the patient. Anorexia had

started when the patient was diagnosed with cancer, but recently, after contraction with COVID-19, it had worsened. There was no history of breathlessness, cough, loose stools, or limb weakness. The patient was diagnosed with a COVID-19 infection in April 2021. According to WHO severity, he had a mild category of disease.^{12,13} He was admitted for his COVID-19 treatment for 14 days without any complications. The patient did not have a history of heart disease, diabetes, or hypertension. He had received three cycles of palliative chemotherapy (Pemetrexed and Carboplatin) for his cancer, and his cancer showed partial response as per response evaluation criteria in solid tumors (RECIST) criteria.¹⁴ The general physical examination and systemic examination of the patient were unremarkable.

Intending to control the common symptoms of pain, anorexia, nausea, and constipation, we started the patient on mild analgesics (paracetamol 650 mg thrice a day), antacids with prokinetic agents (rabeprazole and domperidone). Other symptoms improved with the medications during the follow-up visits, but fatigue was a constant troublesome symptom. He also had occasional bouts of chest pain, myalgia, and sleep disturbances. We performed an investigative panel of

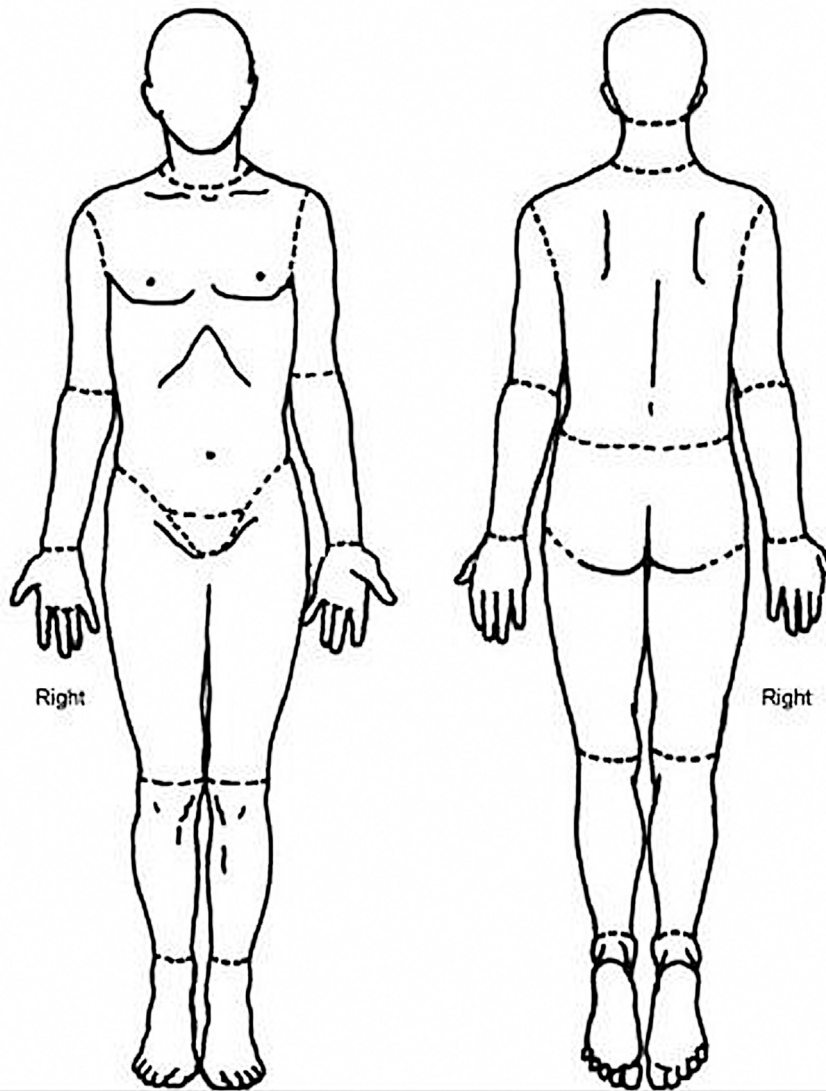
Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Annexure 1 Edmonton symptom assessment scale revised (ESAS-r).

Guidelines – Revised
Edmonton Symptom Assessment System (ESAS-r)

Please mark on these pictures where it is that you hurt:



Annexure 2 Classification of post-COVID-19 syndrome as per Becker et al (COVID-19 clinic of the University of Cincinnati Medical Center).

complete blood count, renal function tests, liver function tests, electrolytes, random blood sugars, thyroid function tests, vitamin D3 levels, and vitamin B12 levels. All other blood investigations were near normal with a minor rise of liver enzymes and lower level of vitamin D3. Apart from the changes of mass in the right lower lobe, the chest X-ray was unremarkable. We diagnosed this case with type 2 post-COVID-19 syndrome (Classification as per Becker [►Annexure 2]).¹⁵ On reviewing the literature, we found megestrol acetate to be one of the off-label drugs used for fatigue in advanced cancer patients. We discussed the risks and benefits of this off-label drug with the patient and relatives, and they consented to the same. On an empirical basis, a low dose of megestrol acetate was initiated. The initial dose of megestrol acetate was 160 mg (per oral) once a day. On initial follow-up after 2 weeks,

there was a 2-point decrease in the fatigue scores subjectively reported by the patient.

Therefore, the dose of megestrol was increased to 160 mg three times a day (per oral). At follow-up of 4 weeks, the patient reported that the fatigue scores significantly decreased to 3/10. The patient could do routine activities, his sleep had improved, and subjectively he was feeling better. Overall, the quality of life of the patient had improved.

Discussion

In December 2019, the world witnessed a pandemic of unknown viral pneumonia, with Wuhan city in China as the epicenter.¹⁶ The etiological agent of this disease was initially named severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2). However, in February 2020, World Health Organization (WHO) renamed it coronavirus disease 2019 (COVID-19).¹⁷ COVID-19 infection is transmitted mainly through the respiratory tract with a very high transmission speed and infectivity.

Most of the patients infected with this virus are asymptomatic, while others present with fever, myalgia, and mild upper respiratory symptoms in the initial phase. In the second phase of the disease, the symptoms worsen. Finally, severe lung inflammation leads to acute respiratory distress syndrome in the third phase.^{12,13} Evidence suggests that the clinical course of COVID-19 is variable, and the symptoms are subjective.^{18–20}

Post-COVID-19 syndrome was first described by Greenhalgh et al²¹ as COVID-19 associated illness extending for more than 3 weeks after onset of the symptoms. The patients have fatigue, breathlessness, olfactory and gustatory dysfunction, chest pain, myalgia, and sleep-related issues. Fatigue among these is the most common symptom, with an incidence in patients ranging from 17.5 to 72%. Various treatment modalities like rehabilitative measures, cognitive measures, nutritional supplements, etc., have been tried to prevent and treat post-COVID-19 fatigue.^{22,23}

Evidence from advanced cancer care settings suggests there is a reduction in cancer-related fatigue using megestrol acetate. For example, Bruera et al¹⁰ reported a significant improvement in overall fatigue score among the patients on the intervention of megestrol acetate compared with the placebo arm. Furthermore, a randomized controlled trial by Mantovani et al⁹ reported a significant difference in the improvement of fatigue scores (Brief Fatigue Inventory Scale) in the arm with megestrol acetate and nutritional supplements compared with the arm with nutritional supplements only ($p = 0.006$).

Megestrol acetate is a progestin and is used as an appetite stimulant among patients with chronic illness. It was introduced in 1971 and approved by United States-Food and Drug Administration (US-FDA) with a specific indication of inducing non-fluid weight gain by increasing body fat but not muscle mass.^{24,25} This drug has been used as a second or third-line therapy agent for advanced carcinoma of endometrium and breast.²⁶ Off-label indications in palliative care settings are anorexia-cachexia syndrome, sweating, and increasing the patient's weight.^{27–29} It has also been used as an agent to reduce hot flushes in postmenopausal women.³⁰ Among the geriatric population with wasting syndrome, this drug improves appetite, elevates pre-albumin levels, and increases weight.³¹ It has an anti-gonadotropic activity which reduces the overall natural steroid synthesis. In addition, it has a suppressive effect on the hypothalamic-pituitary-gonadal axis. One of the hypotheses about megestrol acetate's mechanism of action is that it has inhibitory effects on the in vitro production of cytokines such as tumor necrosis factor, IL-1, and IL-6.^{32,33} This cytokine increase has also been implicated in post-COVID-19 syndrome causing various symptoms. With this purview, we decided to add megestrol acetate to our patient's prescription. As described earlier, once a day dose of this drug had a minor change in the fatigue scores,

but after the dose was increased to three times a day, the improvement was drastic in the next 4 weeks.

Adverse effects of megestrol acetate can be classified into mild and severe. Mild common side effects are nausea, vomiting, rash, loose stools, edema, vaginal bleeding, fluid retention, loss of libido, hypertension, and hyperglycemia.²⁷ Serious side effect profile includes thrombophlebitis, deep vein thrombosis, and sepsis but is rare.²⁷ A minor proportion of patients in post-COVID-19 syndrome experience elevated blood pressure, cardiac arrhythmias, and some gastrointestinal symptoms.^{34,35} This state is also at risk of venous thrombosis. Since the benefit was greater compared to the risks described, we went ahead using this drug for the patient's benefit. Our patient experienced minor side effects like nausea, vomiting, and mild pedal edema throughout the course.

Various drug interactions can be divided into severe, serious, and moderate interactions. Severe interactions have occurred with an anti-arrhythmic drug named dofetilide. Serious interactions causing harmful effects have been described in immuno-modulating drugs like filgotinib and some selected immunosuppressive drugs like leflunomide. The most common moderate interactions with some risks are coumarin anticoagulants like warfarin and dicumarol.³⁶ Various antineoplastic drugs like bleomycin, capecitabine, carboplatin, cisplatin, etc., have minor interactions with megestrol acetate. There are no food interactions documented with this drug.³⁷

The major limitations of the present case are that we will not be able to generalize it, and there is no possibility of a cause-effect relationship. Hence, the current case report is level 4 evidence in the heuristic hierarchy of evidence-based research. Further studies with a larger cohort and randomized controlled trials should be planned in the near future to investigate the efficacy of megestrol acetate in the treatment of post-COVID-19 fatigue. Nonetheless, the present case report is a novel off-label use of megestrol acetate in treating post COVID-19 fatigue.

Conclusion

Our patient was diagnosed to have type 2 post COVID-19 syndrome. Using a small dose (160 mg/d) of megestrol acetate did not improve fatigue in our patient, but it drastically improved after the dose was increased to 480 mg/d. However, the drug's efficacy and the side effect profile have to be studied with randomized controlled trials or more extensive cohort studies to generate a high level of evidence.

Source of Support

None.

Conflict of Interest

None declared.

References

- Rosenthal TC, Majeroni BA, Pretorius R, Malik K. Fatigue: an overview. *Am Fam Physician* 2008;78(10):1173–1179

- 2 Greenberg DB. Clinical dimensions of fatigue. *Prim Care Companion J Clin Psychiatry* 2002;4(03):90–93
- 3 Curt GA. Impact of fatigue on quality of life in oncology patients. *Semin Hematol* 2000;37(4, suppl 6):14–17
- 4 Flechtner H, Bottomley A. Fatigue and quality of life: lessons from the real world. *Oncologist* 2003;8(1, suppl 1):5–9
- 5 Yoo EH, Choi ES, Cho SH, Do JH, Lee SJ, Kim JH. Comparison of fatigue severity and quality of life between unexplained fatigue patients and explained fatigue patients. *Korean J Fam Med* 2018;39(03):180–184
- 6 Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;81(06):e4–e6
- 7 Scordo KA, Richmond MM, Munro N. Post-COVID-19 syndrome: theoretical basis, identification, and management. *AACN Adv Crit Care* 2021;32(02):188–194
- 8 Maltezou HC, Pavli A, Tsakris A. Post-COVID syndrome: an insight on its pathogenesis. *Vaccines (Basel)* 2021;9(05):497
- 9 Mantovani G, Macciò A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010;15(02):200–211
- 10 Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control* 1998;2(02):74–78
- 11 Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7(02):6–9
- 12 Aguilar RB, Hardigan P, Mayi B, et al. Current understanding of COVID-19 clinical course and investigational treatments. *Front Med (Lausanne)* 2020;7:555301
- 13 Thevarajan I, Buising KL, Cowie BC. Clinical presentation and management of COVID-19. *Med J Aust* 2020;213(03):134–139
- 14 Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer* 2016;62:132–137
- 15 Becker RC. COVID-19 and its sequelae: a platform for optimal patient care, discovery and training. *J Thromb Thrombolysis* 2021;51(03):587–594
- 16 Morens DM, Breman JG, Calisher CH, et al. The origin of COVID-19 and why it matters. *Am J Trop Med Hyg* 2020;103(03):955–959
- 17 Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res* 2020;24:91–98
- 18 Bhandari S, Bhargava A, Sharma S, Keshwani P, Sharma R, Banerjee S. Clinical profile of COVID-19 infected patients admitted in a tertiary care hospital in North India. *J Assoc Physicians India* 2020;68(05):13–17
- 19 de Souza R, Mhatre S, Qayyumi B, et al. Clinical course and outcome of patients with COVID-19 in Mumbai city: an observational study. *BMJ Open* 2021;11(05):e042943
- 20 Budhiraja S, Soni A, Jha V, et al. Clinical profile of first 1000 COVID-19 cases admitted at tertiary care hospitals and the correlates of their mortality: an Indian experience. *medRxiv* 2020:2020.11.16.20232223
- 21 Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026
- 22 Maccarone MC, Magro G, Tognolo L, Masiero S. Post COVID-19 persistent fatigue: a proposal for rehabilitative interventions in the spa setting. *Int J Biometeorol* 2021;65(12):2241–2243
- 23 Vink M, Vink-Niese A. Could cognitive behavioural therapy be an effective treatment for long COVID and post COVID-19 fatigue syndrome? Lessons from the Qure Study for Q-Fever Fatigue Syndrome. *Healthcare (Basel)* 2020;8(04):E552
- 24 Balog DL, Epstein ME, Amodio-Groton MI. HIV wasting syndrome: treatment update. *Ann Pharmacother* 1998;32(04):446–458
- 25 Loprinzi CL, Ellison NM, Goldberg RM, Michalak JC, Burch PA. Alleviation of cancer anorexia and cachexia: studies of the Mayo Clinic and the North Central Cancer Treatment Group. *Semin Oncol* 1990;17(6, suppl 9):8–12
- 26 Gill PG, GebSKI V, Snyder R, et al. Randomized comparison of the effects of tamoxifen, megestrol acetate, or tamoxifen plus megestrol acetate on treatment response and survival in patients with metastatic breast cancer. *Ann Oncol* 1993;4(09):741–744
- 27 Yeh S-S, Schuster MW. Megestrol acetate in cachexia and anorexia. *Int J Nanomedicine* 2006;1(04):411–416
- 28 Ruiz-García V, López-Briz E, Carbonell-Sanchis R, Bort-Martí S, González-Perales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. *J Cachexia Sarcopenia Muscle* 2018;9(03):444–452
- 29 Currow DC, Glare P, Louw S, et al. A randomised, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer. *Sci Rep* 2021;11(01):2421
- 30 Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331(06):347–352
- 31 Yeh S, Wu SY, Levine DM, et al. Quality of life and stimulation of weight gain after treatment with megestrol acetate: correlation between cytokine levels and nutritional status, appetite in geriatric patients with wasting syndrome. *J Nutr Health Aging* 2000;4(04):246–251
- 32 Argilés JM, Anguera A, Stemmler B. A new look at an old drug for the treatment of cancer cachexia: megestrol acetate. *Clin Nutr* 2013;32(03):319–324
- 33 House L, Seminerio MJ, Mirkov S, et al. Metabolism of megestrol acetate in vitro and the role of oxidative metabolites. *Xenobiotica* 2018;48(10):973–983
- 34 Saeed S, Tadic M, Larsen TH, Grassi G, Mancina G. Coronavirus disease 2019 and cardiovascular complications: focused clinical review. *J Hypertens* 2021;39(07):1282–1292
- 35 Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* 2020;17(11):1984–1990
- 36 Webmd.com. Interactions of Megestrol acetate [updated 20 Feb 2020]. Accessed November 23, 2021 at: <https://www.webmd.com/drugs/2/drug-8946-8300/megestrol-oral/megestrol-suspension-oral/details/list-interaction-medication>
- 37 Go.drugbank.com. Drug interactions with Megestrol acetate [updated 20 Feb 2020]. Accessed November 23, 2021 at: <https://go.drugbank.com/drugs/DB00351>