



Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Letter to the Editor

Letter to the editor concerning “Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version)” by Zhao et al., Journal of Orthopaedic Translation, 2019, <https://doi.org/10.1016/j.jot.2019.12.004>



Dear editor,

With great interest, we have read “Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version)” by Zhao et al. [1], in which they comprehensively introduce the epidemiology, aetiology, pathology, clinical manifestations, imaging diagnosis, staging and classification, differential diagnosis, nonsurgical treatment, and surgical treatment of osteonecrosis. Following this, we would like to present updated sharing on how to prevent osteonecrosis in the pandemic of novel coronavirus disease 2019 (COVID-19) and the potential strategies linked to novel R&D agents.

Currently, we are facing a global challenge of an outbreak caused by COVID-19. As immunosuppression is likely to be advantageous to avoiding severe complications such as hyperinflammation, many infected patients receive systematic corticosteroid in the treatment of COVID-19. Early on, clinical characteristics were reported in 62 patients infected with COVID-19 in Zhejiang Province, where 16 (26%) patients were given systematic corticosteroid for 3–5 days (40–80 mg/day) [2]. Similarly, in a group of 99 hospitalised patients infected with COVID-19 in Wuhan, 19 (19%) patients were treated with methylprednisolone sodium succinate, methylprednisolone, and dexamethasone for 3–15 days (median 5, range 3–7) [3]. In another retrospective, single-centre study reported in Wuhan, 62 (45%) patients received methylprednisolone with dose and duration varying on disease severity [4]. We agree that life-saving is of the highest priority, yet pulsed or long-term use of corticosteroids would have implications to the musculoskeletal system, especially the well-known steroid-associated osteonecrosis (SAON).

SAON is secondary to systemically administered corticosteroids and/or high-dose daily therapy, particularly in patients with immune-related comorbidities including systemic lupus erythematosus, organ transplantation, rheumatoid arthritis, and severe acute respiratory syndrome [5]. It is pointed out that the long-term effect of joint replacement for SAON may not be as good as that for osteoarthritis or traumatic osteonecrosis due to extensive lesions involving surrounding and distant bones [1]. During the 2002–2003 epidemic of severe acute respiratory syndrome coronavirus (SARS)-CoV1, 254 infected patients were retrospectively studied after receiving steroid treatment in Hong Kong. Magnetic resonance imaging (MRI) outcomes showed that 12 (5%) patients had evidence of subchondral osteonecrosis. Additional nonspecific subchondral and intramedullary bone marrow abnormalities were present in 77 (30%) of 254 patients. This study concluded that the risk of osteonecrosis was 0.6% for patients receiving less than 3 g and 13% for patients receiving more than 3 g of prednisolone-equivalent dose [6].

Fast forward to today. Present time, worse situation. Given the explosive growth of COVID-19-infected population reported by the World Health Organization (191,127 confirmed cases across 160

countries or regions dated March 18, 2020) [7], the consumption of corticosteroid is of serious concern and should be administered strictly. Delaying of corticosteroid restriction would put the overall population infected with COVID-19 at an increasing long-term risk of SAON. So far, the Chinese government has released the latest guidance of diagnosis and treatment of COVID-19 (the 7th version), recommending the restricted use of steroids with the dose of 1–2 mg/kg/day methylprednisolone equivalent for 5 days at most [8]. However, the incidence of SAON could not be completely eliminated so that regular Magnetic resonance imaging (MRI) scan may help as a screening tool to diagnose SAON in early stages after receiving steroid therapy. To reduce the occurrence of SAON, medications such as anticoagulants, fibrinolysis-enhancing drugs, blood vessel dilators, and lipid-reducing drugs have been recommended [1]. In the meantime, cost-effective and safe agents proven in preclinical or clinical studies, for example, XLGB and icaritin derived from herbal medicine, and newly reported combined supplement of magnesium and vitamin C could be translated into a significant force for the future prevention of refractory SAON [9–11].

Funding/support

This work is supported by the Theme-based Research Scheme (Ref No. T13-402/17-N) from the Research Grants Council of Hong Kong, Youth Science and Technology Project from Suzhou Municipal People's Government (Ref No. kjsxw2018034), and Science and Technology Development Fund from Nanjing Medical University (Ref No. NMUB201822).

Conflicts of interest statement

The authors have no conflicts of interest to disclose in relation to this article.

References

- [1] Zhao DW, Zhang F, Wang BJ, Liu BY, Li L, Kim SY, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). *J Orthop Translat* 2019;21:100–10. <https://doi.org/10.1016/j.jot.2019.12.004>.
- [2] Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020;368:m606.
- [3] Chen NS, Zhou M, Dong X, Qu JM, Gong FY, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- [4] Wang DW, Hu B, Hu C, Zhu FF, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J Am Med Assoc* 2020;323(11):1061–9. <https://doi.org/10.1001/jama.2020.1585>.

<https://doi.org/10.1016/j.jot.2020.04.001>

Received 20 March 2020; Accepted 1 April 2020

Available online 25 April 2020

2214-031X/© 2020 The Authors. Published by Elsevier (Singapore) Pte Ltd on behalf of Chinese Speaking Orthopaedic Society. This is an open access article under the

CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

- [5] Xie XY, Wang XL, Yang HL, Zhao DW, Qin L. Steroid-associated osteonecrosis: epidemiology, pathophysiology, animal model, prevention and potential treatments (An overview). *J Orthop Translat* 2015;3(2):58–70.
- [6] Griffith J, Antonio G, Kumta S, Hui DS, Wong JK, Joynt GM, et al. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. *Radiology* 2005;235:168–75.
- [7] World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report-58. Geneva, Switzerland: WHO; 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200318-sitrep-58-covid-19.pdf?sfvrsn=20876712_2. [Accessed 18 March 2020].
- [8] Diagnosis and treatment of novel coronavirus pneumonia - the 7th version.. Beijing, China: National Health Commission of the PRC; 2020. Available at: www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf. [Accessed 3 March 2020].
- [9] Li ZR, Cheng LM, Wang KZ, Yang NP, Yang SH, He W, et al. XLGB herbal Fufang prevents corticosteroid-induced osteonecrosis of the femoral head - a multicenter, randomized, double-blind, placebo-controlled clinical trial. *J Orthop Translat* 2018; 12:36–44.
- [10] Qin L, Yao D, Zheng LZ, Liu WC, Liu Z, Lei M, et al. Phytomolecule icaritin incorporated PLGA/TCP scaffold for steroid-associated osteonecrosis: proof-of-concept for prevention of hip joint collapse in bipedal emus and mechanistic study in quadrupedal rabbits. *Biomaterials* 2015;59:125–43.
- [11] Zheng LZ, Wang JL, Xu JK, Zhang XT, Liu BY, Huang L, et al. Magnesium and vitamin C supplementation attenuates steroid-associated osteonecrosis in a rat model. *Biomaterials* 2020;238:119828.

Haiyue Zu*

Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Shatin, Hong Kong SAR 999077, PR China

Xueting Yi

Department of Medical Imaging, Affiliated Suzhou Hospital of Nanjing Medical University, Soochow 215008, PR China

* Corresponding author. Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, PR China.

E-mail address: 1155116614@link.cuhk.edu.hk (H. Zu).