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Comments on: "Long-term efficacy of mesenchymal stem cell treatment for complex perianal fistulas: A systematic review and meta-analysis"

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Abstract

The meta-analysis by Wang et al. aimed to assess the long-term effects of mesenchymal stem cells on complex perianal fistula. The authors concluded that mesenchymal stem cell therapy has a long-term effect on the clinical response of complex perianal fistula and should be widely promoted not only in adults but also in infants and adolescents; however, more research on this topic is needed. We appreciate the authors' hard work, and we also agree with this argument. However, we have several concerns about the study. We think it is necessary to discuss the effect of anti-TNF and immunosuppressive therapy on the effcacy of mesenchymal stem cell treatment for perianal fistula in future trials, in order to optimize treatment strategies in perianal fistula patients and reduce the economic burden of patients. In the future, it will be interesting to assess the safety and feasibility of injection of fibrin glue combined with mesenchymal stem cells in perianal fistula.

Key words: *perianal fistulas, mesenchymal stem cell, long-term efficacy, systematic review and meta-analysis.*

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We read with great interest the study by Wang *et al*. [1], who aimed to assess the long-term effects of mesenchymal stem cells (MSCs) on complex perianal fistulas (PFs). We appreciate the authors' hard work. Also, we have a few comments on the article. First, the meta-analyses indicated that MSC therapy has a long-term effect on the clinical response of complex PFs. We agree with this argument. To date, MSCs have been used as a tolerable and potentially effective second-line therapy for steroid-refractory acute graft-versus-host disease (SR-aGVHD). Also, MSC therapy has been approved for paediatric and adult patients with SR-aGVHD. The study by Jiang *et al*. indicated that combining MSC treatment with the best available care for patients with SR-aGVHD, particularly those with gut involvement, may provide the greatest benefit by swiftly controlling peak inflammatory responses within days and facilitating immune modulation and the repair of immunological damage within weeks [2]. The study by Cheng *et al*. [3] also aimed to evaluate the long-term efficacy and safety of MSCs for PF treatment. The authors stated that local MSC therapy promotes long-term and sustained healing of complex PFs and this method is safe. Second, most patients with Crohn's disease (CD) included in the study of Wang *et al*. were receiving either infliximab or adalimumab at the time of MSC injection. MSCs were used together with anti-tumor necrosis factor (TNF) in some clinical studies and they share common targets. Their interaction should be studied carefully. The study by Sakha *et al*. [4] indicated that as an anti-TNF-α agent, infliximab can decrease the inflammation in the microenvironment of MSCs, which might mitigate the immunomodulatory effects of MSCs. However, the study by Duijvestein *et al*. [5] showed that the exposure of MSCs to physiological concentrations of anti-TNF agents does not affect their survival and their inhibitory effects on peripheral blood mononuclear cell proliferation. So, it is necessary to explore the interaction between treatment approaches in order to optimize treatment strategies in PF patients and reduce the economic burden of patients. Wang *et al*. [1] did not discuss the effect of anti-TNF and immunosuppressive therapy on the efficacy of MSC treatment for PFs. So, we think it was the limitation of this study. Finally, cells can be carried through fibrin glue, which acts as a temporary matrix that favours cell-matrix interactions and allows local and paracrine functions of MSCs. In the study by Wang *et al*., some included articles reported efficacy of local fi-

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brin glue combined with MSC therapy for PFs. Whether there was any promotion effect of the MSCs plus fibrin glue therapy remains unknown. Hence, it will be interesting to assess the safety and feasibility of injection of fibrin glue combined with MSCs in PFs. In the future, RCTs are needed to directly compare the long-term effectiveness and safety between MSCs, immunomodulators, biologics, and combination therapies for PFs. This will help the treating physician to determine the optimal disease management strategy.

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Disclosures

Approval of the Bioethics Committee was not required. The author declares no conflict of interest.

References

1. Wang T, Li M, Shang H, et al. (2024): Long-term efficacy of mesenchymal stem cell treatment for complex perianal fistulas: A systematic review and meta-analysis. Cent Eur J Immunol 49: 273-281.
2. Jiang E, Qian K, Wang L, et al. (2024): Efficacy and safety of human umbilical cord-derived mesenchymal stem cells versus placebo added to second-line therapy in patients with steroid-refractory acute graft-versus-host disease: a multicentre, randomized, double-blind, phase 2 trial. BMC Med 22: 555.
3. Cheng F, Zhong H, Huang Z, Li Z (2023): Up-to-date meta-analysis of long-term evaluations of mesenchymal stem cell therapy for complex perianal fistula. World J Stem Cells 15: 866-875.
4. Sakha YA, Ehsani E, Roshandel E, et al. (2012): Assessment of the effect of infliximab on immunomodulation properties of mesenchymal stem cells in vitro. Adv Pharm Bull 11: 739-745.
5. Duijvestein M, Molendijk I, Roelofs H, et al. (2011): Mesenchymal stromal cell function is not affected by drugs used in the treatment of inflammatory bowel disease. Cytotherapy 13: 1066-1073.