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Case report

Osteonecrosis of the jaw associated with ustekinumab in the treatment of Crohn's

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ABSTRACT

MRONJ is a well-known side effect of antiresorptive and antiangiogenic drug treatment. Crohn's disease involves pro-inflammatory interleukins IL-12 and IL-23. Ustekinumab is a targeted therapy antagonist of the p40 subunit of IL-12 and -23 indicated in the treatment of immune-mediated inflammatory diseases.

A 72-year-old man with Crohn's disease developed MRONJ after being treated with ustekinumab for four years. The patient presented with bone exposure three months after the extraction of two mandibular teeth. He had no known predisposing factors and never received ARDs. The patient underwent surgical treatment, and ustekinumab treatment was suspended for six months. No recurrence of MRONJ was detected after 12 months.

Although the new definition of MRONJ excludes antiangiogenic molecules, tyrosine kinase inhibitors, and mTOR inhibitors alone, some cases have been reported with ustekinumab. This report highlights the possibility of MRONJ occurring when taking ustekinumab for Crohn's disease, even without being treated with antiresorptive drugs.

1. Introduction

Since 2003, MRONJ has been a well-known side effect of antiresorptive drug (ARD) treatment. Those treatments are used for oncologic and non-oncologic diseases.

Many other drugs, such as antiangiogenic drugs and other targeted therapies, have been implicated more recently. According to the 2022 AAOMFS definition, MRONJ corresponds to the presence of exposed necrotic bone or bone that can be probed through an intraoral or extra-oral fistula in the maxillofacial region, that has persisted for more than eight weeks, in a patient who is or has been treated with ARDs alone or in combination with immune modulators or antiangiogenic medication with no history of radiation therapy or metastatic disease to the jaws [1].

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD). The origin of CD could be an aberrant immune response to the microbiota [2].

Pro-inflammatory interleukins (IL)-12 and IL-23 are involved in the pathogenesis of chronic mediated inflammatory diseases.

Tumour necrosis factor (TNF-α) inhibitors and antagonists of IL-23 and IL-12 are targeted therapies used in the treatment of immune-mediated inflammatory diseases. Ustekinumab is an antagonist of the p40 subunit of IL-12 and -23.

Some cases of MRONJ are described in the literature after using ustekinumab, in association with TNF-α inhibitors, and without

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ARD treatment, unlike the new definition of MRONJ.

This report aimed to highlight the possibility of MRONJ when using ustekinumab for Crohn's disease, without having been treated with ARDs.

2. Case report

A 72-year-old man presented with a 3-months bone exposure after extraction of teeth 37 and 47 for endo/periodontal disease. He had been treated with ustekinumab every eight weeks for four years.

His past medical history included Crohn's disease.

He first received adalimumab and methotrexate for four years, followed by vedolizumab for one year. Ustekinumab was started on July 2017 and administrated every eight weeks. Those treatments were used in combination with corticosteroids. The patient never received ARDs. No predisposing factor for osteonecrosis was identified such as poor oral health, diabetes, tobacco and alcohol consumption.

The only risk factor could be an endo/periodontal disease, for which the patient was treated.

Uneventful mandibular extractions were performed by his dentist for infection on 20 May 2021 (tooth 47) and 9 June 2021 (tooth 37) (Fig. 1). Those extractions were realised during ustekinumab treatment (last dose five days before the first extraction). No antibiotherapy was administered before and after extraction.

Three months after extraction (25/08/2021), the patient presented at the maxillofacial department. At clinical examination, bone was exposed on the two extraction sites behind the teeth 36 and 46 (Fig. 2). No pus discharge, no mobility of the adjacent teeth (36 and 46), no swelling of the mucosa, no intraoral or extraoral fistula were observed. The last dose of ustekinumab was administered on August 15, 2021.

A CBCT showed persistence of unhealed extraction sites with the presence of sequestra and osteocondensation in the 2 areas, and involving teeth 36 and 46 (Figs. 3 and 4).

The two lesions were classified as stage 1 MRONJ according to the AAOMS staging system.

After discussion with the gastroenterologist, ustekinumab treatment was suspended twelve weeks before surgical treatment under general anaesthesia. Debridement of the necrotic tissues and curettage of the two sites were realised, associated with the extraction of teeth 36 and 46.

The bone surfaces were smoothed with a piezotome.

The surgical sites were filled with L-PRF and sutured hermetically after the elevation of a mucoperiosteal flap and periosteal incision, to avoid tissue tension. Mouth rinses with chlorhexidine 0,12 % and H2O2 3 % were performed before and after surgery until mucosal healing. Antibiotic therapy (amoxicillin 875 mg – clavulanic acid 125 mg) was started 1 h before surgery (two tablets) and continued twice a day for ten days.

Post-operative evolution was uneventful and one month after surgery, mucosal healing was complete on both sites.

The histopathological examination confirmed the diagnosis of osteonecrosis with the presence of Actinomyces.

Control CBCT was realised 3 months after surgery. Since there was no suspected image and the patient was asymptomatic, ustekinumab was reintroduced. No recurrence was observed 16 months after surgical treatment. The patient did not experience an acute episode of CD during treatment discontinuation.

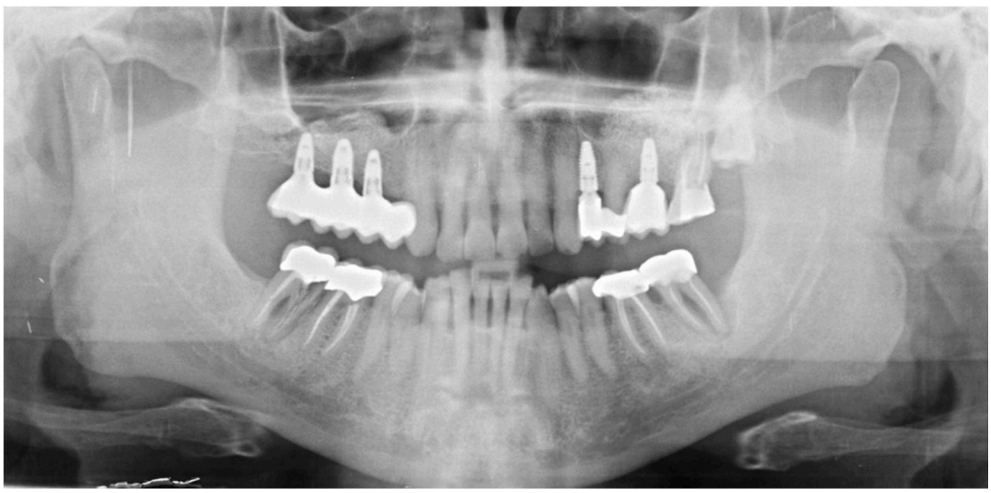

Fig. 1. Panoramic X-ray: endo/periodontal disease on teeth 37 and 47.

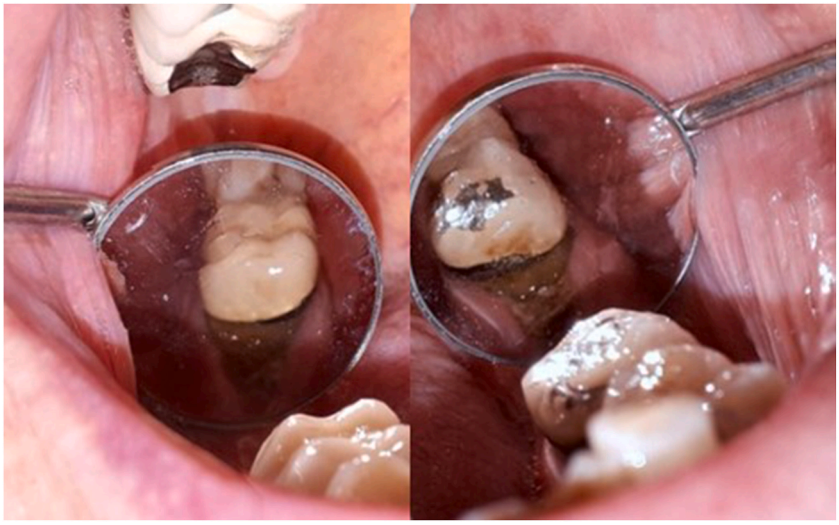

Fig. 2. Oral view: bone exposure of the extraction sites of teeth 37 and 47, with loss of posterior bone anchorage of the roots of teeth 36 and 37.

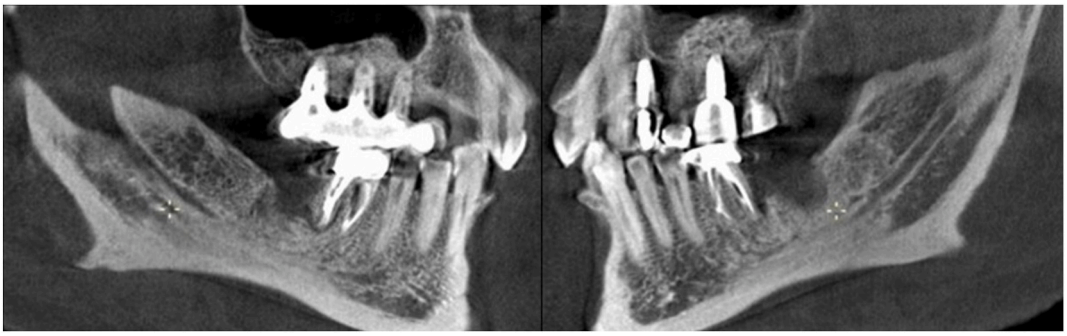

Fig. 3. CBCT: parasagittal view: no bone reconstruction 3 months after extraction of teeth 37 and 47, osteocondensation and bone loss around posterior roots of teeth 36 and 46.

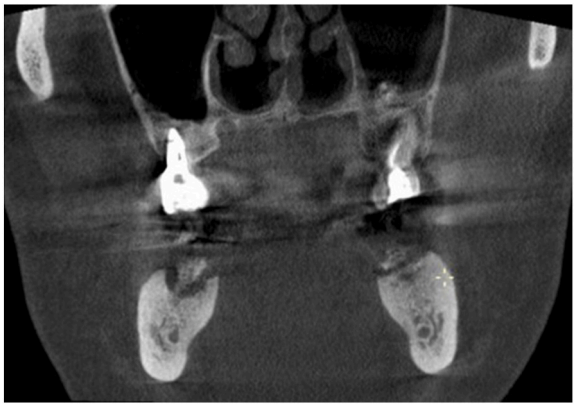

Fig. 4. Coronal CBCT: presence of bone sequestration (white arrows) and osteocondensation at both extraction sites.

3. Discussion

MRONJ is a known side effect of bisphosphonates and denosumab. Although the new definition of the AAOMS excludes MRONJ with antiangiogenic molecules, tyrosine kinase inhibitors, and mTOR inhibitors alone, some cases are described in the literature

outside the administration of ARDs. Some MRONJ cases have been described in patients treated for CD with TNF-α inhibitors (infliximab, adalimumab …) [3].

Recent advances in biology and genetic engineering have led to the development of chimeric, humanised and fully human

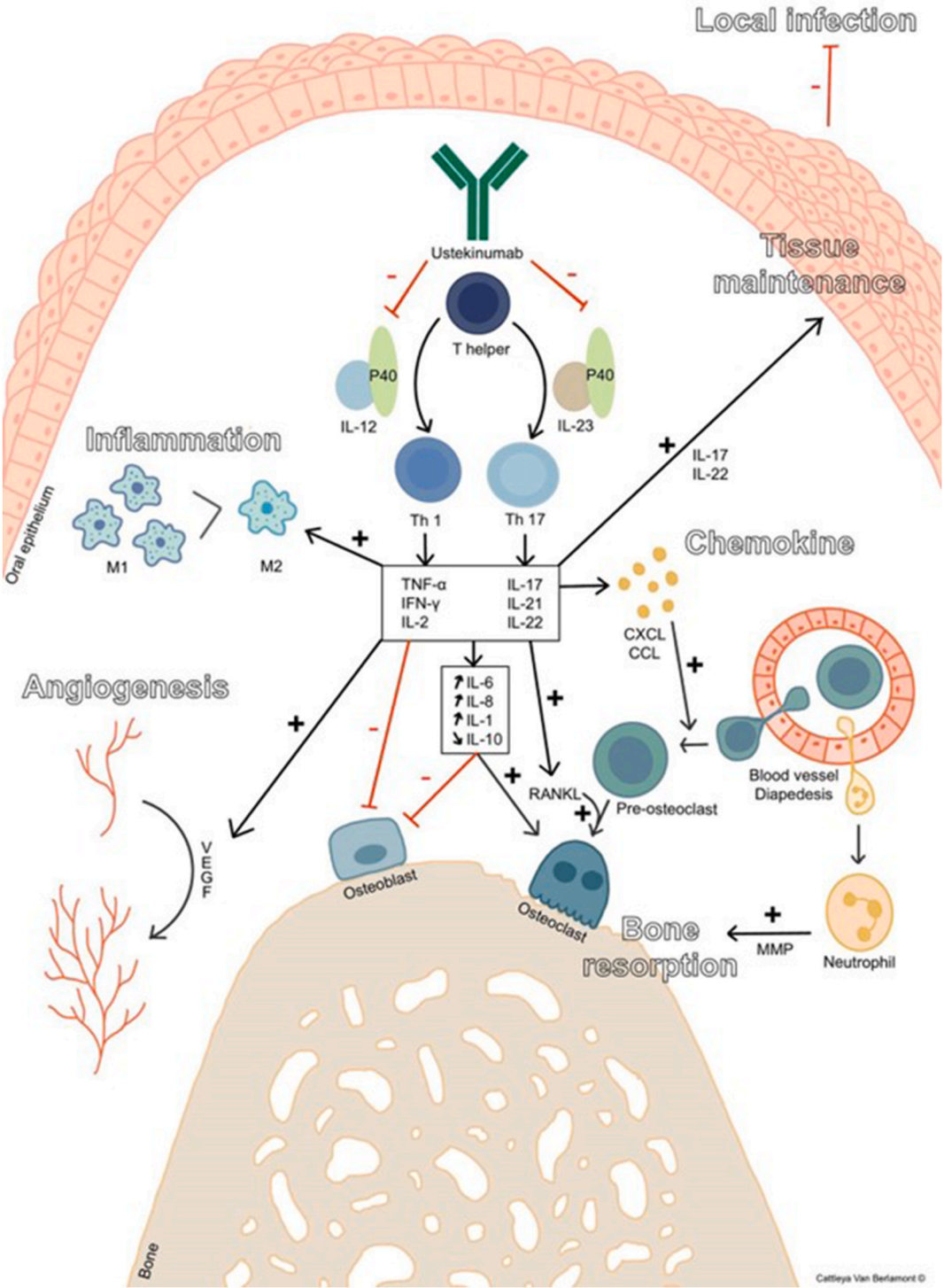

Fig. 5. Diagram illustrating the impact on the different biological functions involved in the pathogenesis of MRONJ (bone resorption; soft tissue toxicity; inhibition of angiogenesis; immunosuppression and local infection). M1: M1 macrophage (pro-inflammatory and osteoclastogenic); M2: M2 macrophage (anti-inflammatory and pro-osteogenic); MMP: matrix metalloproteinases.

therapeutic monoclonal antibodies (mAbs) to treat various diseases.

Ustekinumab is a human IgG1 kappa mAb that was approved by the Food and Drug Administration (FDA) for the treatment of psoriasis in 2009. The FDA extended its indication to include the treatment of psoriatic arthritis, inflammatory bowel diseases (IBD) and psoriasis in adolescents.

Ustekinumab binds to the p40 subunit common to IL-12 and IL-23 and prevents their interaction with the IL-12 receptor β1 subunit of IL-12 and IL-23 receptor complexes.

IL-12 and IL-23 induce the differentiation of $CD4^+$ naïve T cells to CD4 Helper cells into Th1 and Th17 cells, respectively. Consequently, ustekinumab affects the polarisation of CD4 + naïve T cells to CD4 Helper cells type 1 (Th1) and type 17 (Th17) T lymphocytes (Fig. 5).

Th1 and Th17 cells can produce effector cytokines (CKs).

Th1 cells produce TNF-α, interferon gamma (IFN-γ) and IL-2, while Th17 cells produce IL-17A, IL-17F, IL-21 and IL-22, as well as growth factors such as macrophage colony-stimulating factor (M-CSF). Th1 and Th17 CKs can induce the production of vasodilators, chemokines (CXCL, CCL) and the expression of adhesion molecules on endothelial cells. This process promotes monocyte and neutrophil recruitment, T-cell infiltration, neovascularization, keratinocyte activation and hyperplasia, but also contributes to bone resorption (Fig. 5).

Ustekinumab is commonly used to treat autoimmune diseases such as IBD, psoriasis, and psoriatic arthritis. These conditions are known to involve two specific pathways (IL-12/Th1 and IL-23/Th17), which are often implicated in the development of autoimmune disorders.

Recent progress in osteoimmunology has improved our comprehension of how bone tissue and the immune system interact, considering their close association, especially as immune cell maturation occurs in the bone marrow. It is now improbable that bone formation and destruction mechanisms occur without immune cells.

In MRONJ caused by bisphosphonates (BPs), immune-bone interaction is affected, leading to bone homeostasis imbalance and decreased turnover [1]. This new approach allows us to understand how the immune system influences bone tissue remodelling, vascularization, healing and infection resistance, all factors involved in the development of MRONJ. Inhibition of IL-12/Th1 and IL-23/Th17 pathways disrupts various alveolar bone biological functions, potentially contributing to MRONJ pathogenesis.

At the level of bone resorption: the immune system and interleukins play a key role in modulating the balance between bone-building cells (osteoblasts) and bone-destructive cells (osteoclasts) [4].

This regulation may or may not involve the RANK pathway directly or indirectly.

The interaction between CKs and ustekinumab are described in Table 1.

As explained above, IL-12 and IL-23 induce the differentiation of T cells into Th1 and Th17 cells, respectively. This results in the production of CKs such as TNF-α and IFN-γ by Th1 cells, and IL-17F, IL-21, IL-22, and M-CSF by Th17 cells. These CKs have inhibitory effects on bone resorption through direct or indirect mechanisms, RANKL pathway-dependent or not, and can also influence osteoblast activity (Fig. 5) [5].

The production of IL-1, IL-6, IL-8 and other chemokines is increased, which can affect the recruitment of pre-osteoclasts, while the levels of the anti-inflammatory and pro-osteogenic CK IL-10 are decreased.

Blocking IL-12 and IL-23 influence the polarisation of macrophage into M1 type (pro-inflammatory and osteoclastogenic) and M2 type (anti-inflammatory and pro-osteogenic), with an increased M2/M1 ratio [6].

This change in the osteoimmune microenvironment continues to alter the homeostasis balance of alveolar bone [7].

A clinical example of how a molecule can modify the homeostatic balance of alveolar bone is the use of ustekinumab. Ustekinumab can stabilise a genetic periodontal disease induced by leukocyte adhesion deficiency [8].

In summary, the reduced bone resorption and the turnover led to a hypermineralised bone, as shown in Figs. 3 and 4. This modification of the bone microenvironment towards an osteopetrotic bone cannot provide sufficient vascularization to the jaw, so MRONJ can occur as a result of changes in the external environment [9].

Concerning soft tissue toxicity: in addition to the inhibition of bone remodelling, soft tissue toxicity is also described. Mucosal ulcerations may be the initial pathological event that occurs in MRONJ [1]. IL-17 has a well-recognized role in immune surveillance at the epithelial level. Together with IL-22 (produced by Th17 cells), IL-17 ensures the maintenance of epithelial tissue integrity (notably via the production of the tight junction protein claudin) (Fig. 5) [10].

Concerning inhibition of angiogenesis: the development of MRONJ can also be promoted by the inhibition of angiogenesis. Various CKs such as IL-23, IL-17, IL-22, IL-6, IL-8, IL-1β and TNF-α are potent angiogenesis stimulators. This action is mediated by the enhancement of VEGF production but also via indirect mechanisms [11]. Anti-IL-23 mAb or anti-IL-17 mAb intravitreal injections have been found to reduce retinal neovascularization in mice. Ustekinumab treatment was also shown to downregulate VEGF in the joints of arthritic patients (Fig. 5) [12].

Concerning immunosuppression: local infection, more than tooth extraction, is a significant risk factor for MRONJ development [1]. Ustekinumab, acting as a CK modulator, could decrease the immune response to clear local infections and potentially reduce the risk of MRONJ.

In conclusion, the immune system plays a central role in the development of MRONJ, and its dysfunction may contribute to the disease. In this case report, the bilateral presentation of MRONJ suggests a systemic problem related to ustekinumab rather than an unfortunate coincidence event that mimics MRONJ.

Interleukins, produced by immune cells, play a role in the complex pathogenesis of MRONJ, and the specific immune pathways leading to MRONJ may vary depending on the drug used.

However, it is possible that several pathways are implicated and that the immune pathways by which MRONJ occurs are different

Table 1
Interaction between CKs and ustekinumab.

Pro-osteoclastogenic and pro-inflammatory CKs	IL-1[a], IL-6[a], IL-7, IL-11, IL-15, IL-17[a], TNF-α[a], TNF-β[a], RANKL[a] and M-CSF[a]
Pro-osteogenic and anti-inflammatory CKs	IL-4, IL-5, IL-10[b], (IL-12[c]), IL-13, IL-18, (IFN-γ[c]), TGF-β and OPG

[a] Decreased by ustekinumab treatment.
[b] Increased by ustekinumab treatment.
[c] Decreased by ustekinumab treatment but may indirectly promote osteoclastogenesis in some circumstances.

depending on the drug involved. In other words, MRONJ caused by BPs, anti-RANKL antibodies, or mTOR inhibitors are immunologically distinct, that is to say that the immune pathways are not necessarily identical or even opposite depending on the molecule. It introduces an additional level of complexity to our comprehension of the immunology of MRONJ.

Although, ustekinumab can be considered as an immunologic treatment for periodontitis which is often involved in MRONJ pathogenesis [13]. From an osteoimmunological perspective, it appears to be a contradiction between the use of ustekinumab and periodontal disease.

MRONJ related to ustekinumab may be considered "hypoinflammatory" and potentially less aggressive. However, the management of MRONJ related to ustekinumab should not differ from the "classic" MRONJ.

As recommended in case of digestive surgery, one could suggest stopping ustekinumab treatment four weeks before jaw surgery and restarting it four weeks after surgery, or until total mucosal recovery.

However, this duration is arbitrary and based on the drug's half-life of three weeks. But the duration of ustekinumab's imprint on the immune system and its effects on lymphocyte reprogramming is not fully understood. Determining the hierarchy of factors promoting stability or plasticity following ustekinumab treatment is crucial to make less arbitrary recommendations on therapeutic holidays. It cannot be excluded that long-term anti-TNF treatment may have had an imprint on the functioning of the immune system in this case report. We recommend a dental check-up before starting ustekinumab. A follow-up of patients treated with ustekinumab would be useful to monitor the occurrence of new cases of MRONJ.

CRediT authorship contribution statement

Jean Massaad: Writing – original draft. **Michèle Magremanne:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Massaad Jean reports was provided by University Hospital Saint-Luc. Massaad Jean reports a relationship with University Hospital Saint-Luc that includes: employment. Massaad Jean has patent Dr pending to Licensee. no If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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