BONE

# Arginine restriction attenuates bone loss in arthritis

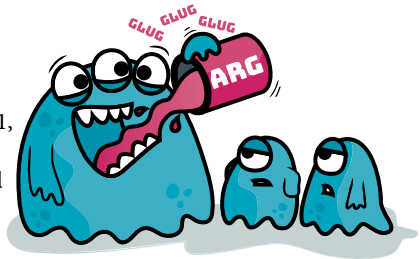
Aberrant bone resorption by osteoclasts causes bone destruction in joint diseases such as rheumatoid arthritis (RA). The generation of osteoclasts is influenced by cytokines in the surrounding environment, such as receptor activator of NF-κB ligand (RANKL), and might also be affected by extracellular nutrients. A new study published in *Nature Communications* shows that depletion of the amino acid arginine attenuates osteoclastogenesis and ameliorates arthritis in mice.

"We previously showed that arginase 1 was actively secreted by alternatively activated macrophages in the context of autoimmunity," explains Gernot Schabbauer, co-corresponding author on the new study. "This finding led us to believe that arginase 1-mediated extracellular arginine degradation could be important in regulating autoimmunity, by dampening immune cell metabolism."

To test whether depletion of systemic arginine could alter cellular metabolism in bone and impede the progression of inflammatory arthritis, the authors investigated the effects of a recombinant modified form of arginase 1 (recArg1) in vitro and in mouse models of disease.

> "depletion of the amino acid arginine attenuates osteoclastogenesis"

"By combining mouse models of arthritis with omics approaches (transcriptomics, proteomics and metabolomics) in the presence and absence of recArg1, we showed that RANKL-mediated osteoclastogenesis depends on extracellular arginine," says co-corresponding author Stephan Blüml. "Systemic arginine restriction improved outcomes in diverse mouse arthritis models, especially regarding osteoclast-mediated bone destruction."



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Arginine depletion prevented the transcriptional and metabolic effects of RANKL and led to metabolic quiescence of osteoclast precursor cells. The effects of arginine restriction on osteoclast formation were reversible, and arginine precursors could compensate for their absence.

"We plan to test the importance of extracellular arginine depletion in other multinucleated giant cell-mediated diseases," explains Schabbauer. "Looking into the future, our work might pave the way to test dietary interventions such as avoidance of arginine-rich food for arthritis management," concludes Blüml.

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**ORIGINAL ARTICLE** Brunner, J. S. et al. Environmental arginine controls multinuclear giant cell metabolism and formation. *Nat. Commun.* **11**, 431 (2020)

RHEUMATOID ARTHRITIS

# EULAR updates its RA management recommendations

EULAR has updated its recommendations for the pharmacological management of rheumatoid arthritis (RA) with DMARDs to reflect developments since the previous update in 2016, including the approval of several new drugs and the accumulation of long-term safety and efficacy data. Major changes had not been anticipated, and indeed most of the recommendations remain unchanged. "If one looks at the EULAR recommendations from their first presentation exactly one decade ago and throughout the updates in 2013 and 2016, one can see that this combination of evidence and expert opinion has stood the test of time," remarks lead author Josef Smolen.

In the latest update, which is based on systematic literature reviews and the opinions of experts from around the world, the target of treatment remains as sustained remission (according to the ACR–EULAR definition) or low disease activity. This goal is considered achievable for most patients with RA, but might require cycling through multiple different drugs. Moreover, although guidance is provided on the tapering of medication for patients who achieve sustained remission, it is also recognized that many patients will require lifelong treatment.

> The recommendations provide a sequential treatment strategy

The recommendations provide a sequential treatment strategy, as summarized in an algorithm that provides a general overview. "The algorithm divides the therapeutic cascade into three phases: initial approach, failure of methotrexate plus glucocorticoids, and failure of a first biologic or targeted synthetic DMARD," notes Smolen.

The initial DMARD strategy remains methotrexate plus glucocorticoids. If the treatment target is not achieved and unfavourable prognostic markers are present, a biologic or targeted synthetic DMARD should be added; in a change from the previous update (which favoured biologic over targeted synthetic DMARDs), preference is not given to either type of DMARD, in light of evidence of the efficacy and safety of JAK inhibitors.

The task force behind the recommendations also provided an updated research agenda to highlight important issues to address in future updates, including the safety and efficacy of various sequences and combinations of drugs, the need for biomarkers to stratify patients and predict therapeutic response, and the reasons for secondary loss of efficacy.

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**ORIGINAL ARTICLE** Smolen, J. S. et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2019-216655 (2020)