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### Closing the Gap between Preclinical Biologic Development and Clinical Application in Rheumatoid Arthritis

The Editor,

Sir,

Rheumatoid arthritis (RA) is a chronic autoimmune disease; deferment and relapse of aggressive synovitis finally leads to destruction of joint cartilage and bone, and that is the main hazard of the disease. In recent years, biologic agents have become a hot spot of RA treatment research, owing to their higher specificity and fewer side effects than existing non-biologic disease-modifying and anti-inflammatory drugs. Although experimentally-induced arthritis models of rhesus monkeys are considered to be the closest model to the human RA disease (1), in the evaluation of preclinical biologic therapeutics, whether the disease also relapses in rhesus monkey models and

the correspondent treatment efficacy in that condition were rarely studied. The reason for this phenomenon is that it was considered that induced-arthritis in rhesus monkeys is a monophasic course, and findings in previous studies also seemed to accord with this opinion: most common surrogate markers for the rhesus monkey model, *ie* clinical scoring, inflammatory and immunological markers, returned to the normal range within a typical follow-up time (70 days) after disease induction (2).

However, nowadays, in addition to the aforementioned traditional markers, a more sensitive imaging method, magnetic resonance imaging (MRI) with features of high soft-tissue resolution, multisection and multiparameter, has the unique advantage of being able to visualize the subclinical inflammatory synovium in clinical studies (3). In RA patients in remission according to the 28-joint Disease Activity Score-C-reactive protein (DAS28-CRP), persistent active synovial inflammation detected by MRI is a high-risk predictor of subsequent joint destruction (4). Therefore, high-sensitivity MRI may give a deeper understanding in experimentally-induced arthritis in rhesus monkeys. In our previous study, we used MRI for dynamic evaluation of small hand joints in induced-arthritis models of rhesus monkeys treated with Celebrex (celecoxib). On day 90 after disease induction, MRI still revealed active synovitis in small hand joints in some monkeys (Figure), but common markers (*ie* clinical scoring and CRP) had returned to normal.

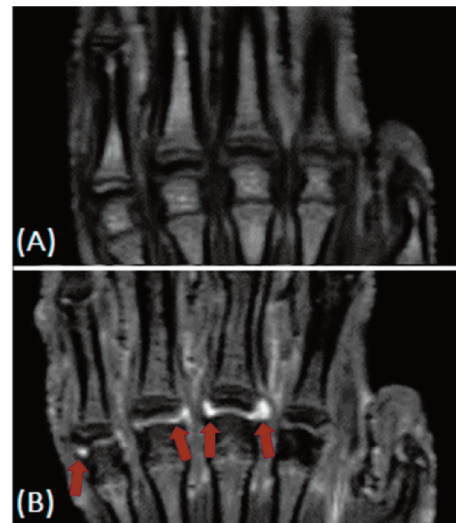


Figure: Magnetic resonance imaging (MRI) of small hand joints in rhesus monkeys with induced-arthritis.

Comparing the condition of pre-induction (A) and 90 days post-induction (B) rhesus monkey model in coronal enhanced T1-weighted images: before disease induction, the metacarpophalangeal joints (MCPs) were normal and there was non-enhancement in synovium; on 90 days post-induction, although most common markers of disease returned to normal: clinical scoring range within 0–1 point and CRP value below 1 mg/L, multiple active synovitis in MCPs (arrow) can still be found in MRI, indicating the continuous chronic activity in rhesus monkeys of induced-arthritis models after 90 days post-induction.

These data suggest that the sensitivity of conventional indicators may be insufficient, leading to a lack of awareness

of changes in the disease of rhesus monkey models. The clinical significance of induced-arthritis models of rhesus monkeys to the study of the chronic course of RA may be underestimated.

Therefore, sensitive imaging detective method MRI is essential to further preclinical studies. The more accurate method may play a critical role in the evaluation of disease progression and prognosis in induced-arthritis model of rhesus monkeys. This is beneficial not only to help identify proper models that are more consistent with the human RA chronic disease progression, but also to ascertain clinical significance in new biologic agent therapy strategy.

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**Keywords:** Magnetic resonance imaging, rhesus monkey, rheumatoid arthritis

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