# Rheumatology's Most Impactful Discoveries This Year

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**Citation:** AMJ Rheumatol. 2024;1[1]:19-23. https://doi.org/10.33590/rheumatolamj/JUPL9045.

EXPERTS at the American College of Rheumatology (ACR) Convergence 2024 identified and showcased the most groundbreaking discoveries in the field of rheumatology in the last 12 months in a session titled "Year in Review: Clinical Science".

Tasked with presenting the key advances in clinical sciences for 2024, Michael Pillinger, New York University Grossman School of Medicine, New York, was introduced as someone known by the entire community as a master educator and recipient of numerous prestigious honors. As with all scientific presentations, Pillinger opened the session with his disclosures; however, he quickly set an engaging tone by stating that his real disclosure is that "there is just no way I could possibly present all of the great work that's transpired this year. So, I'm just going to start out with an apology for the other 99% of clinical research that I won't be including."

## RHEUMATOID ARTHRITIS

Taking the audience on a journey through a range of scientific advancements in rheumatological diseases, Pillinger began with rheumatoid arthritis (RA). He specifically drew attention to pre-RA and the ongoing goal to identify at-risk patients before disease onset: can RA be prevented by pre-clinical intervention? Several studies published this year have aimed to answer this question, albeit with "murky" results, explained Pillinger. He noted that finding the optimal treatment window and the optimal therapeutic agent is key.

A potential candidate that has been at the heart of several studies this year has been abatacept, a selective co-stimulation modulator with inhibitory activity on T lymphocytes. The APIPPRA trial, a Phase IIb clinical study, investigated the efficacy of abatacept in individuals at high risk of developing RA.[1] Participants received either 125 mg of subcutaneous abatacept weekly or a placebo for 12 months. At 24 months, 25% of participants in the abatacept group had progressed to RA, compared to 37% in the placebo group. Additionally, abatacept demonstrated improvements in pain, functional well-being, and quality-of-life measures, as well as reduced levels of subclinical synovitis.

Similarly, in the ARIAA trial, high-risk adults received weekly subcutaneous abatacept 125 mg or placebo for 6 months, followed by a drug-free, observation phase for 12 months.[2] The results revealed that 6-month treatment with abatacept reduces inflammation, clinical symptoms, and the risk of developing RA in high-risk individuals. Notably, the benefits persisted throughout a 1-year drug-free observation phase.

Interestingly, Pillinger noted, a substantial number of patients receiving abatacept,


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in both studies, immediately went on to develop RA. This can be looked at from two perspectives: either abatacept may have been effective in delaying the onset of RA, or it may have ultimately failed to prevent its development. However, by the end of both studies, particularly in the ARIAA trial, there was still a significant difference between the placebo and abatacept groups, and a meaningful number of patients who received abatacept never went on to develop RA.

## GOUT

Pillinger transitioned from the most common autoimmune arthritis, RA, to the most common inflammatory arthritis in the US: gout. Drawing attention to the link between gout and cardiovascular (CV) risk, he emphasized the need for early CV risk management in these patients.

Patients with gout have about a two-fold increase in CV risk, including myocardial infarction (MI), compared to the general population. Generally, this increased risk has been attributed to the chronic, long-standing impact of having an immune or inflammatory disease. However, a few years ago, it was observed that patients who experienced a gout flare had a significantly increased risk of MI and stroke for up to 120 days after the flare, indicating a pathological change that persisted after the flare.[3] This year, the same research group reported the short-term risk of CV events in people newly diagnosed with gout.[4] The results demonstrated that the incidence of cardiovascular events in the 30 days following a first gout diagnosis was significantly higher than in the subsequent 31–730 days after gout diagnosis. These findings support the need for attentive CV risk management in patients with gout, particularly within the first 30 days.

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## OSTEOARTHRITIS

Shifting now from the most common inflammatory arthritis to the most common arthritis overall, osteoarthritis (OA). Pillinger focused on knee OA, describing it as a condition that often makes clinicians "put our hands up to our heads and scream, because it's our most common disease, but we're so bad at managing it. We only treat the symptoms and send them to the surgeons." However, there may be change on the horizon, as Pillinger highlighted a substantial number of clinical trials on knee OA that were published this year.

There have been a number of methotrexate studies over the last few years that suggest a possible benefit in OA. For example, the PROMOTE trial revealed that at 6 months, methotrexate was statistically superior to placebo in reducing knee pain.[5] Other outcomes of function and stiffness were also significant compared to placebo at 6 months. However, there were some limitations in the study. For example, with a different pain scale, the Womack score, the observed difference was not statistically significant. Importantly, the significant difference observed was lost at the 12-month mark.

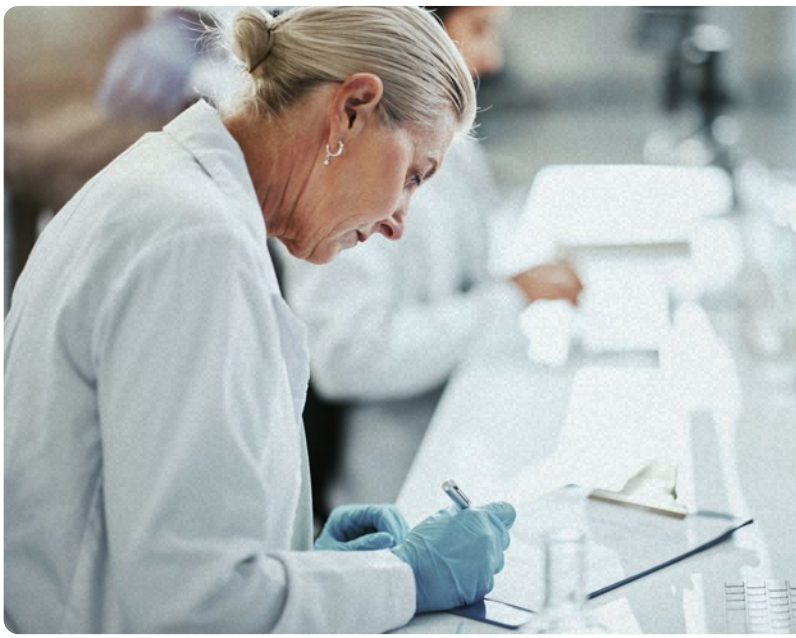
## LUPUS, MYOSITIS, AND SYSTEMIC SCLEROSIS

Humorously, Pillinger admitted that lupus, myositis, and systemic sclerosis are not usually diseases you would put together in a presentation due to their distinct pathologies. However, he noted, one element that ties these complex conditions together is an approach that aims to treat them all: CD19 CAR-T cell therapy.

Pillinger gave credit to a study by Müller et al.[6] for "taking CAR-T cell therapy out of oncology and into rheumatology". In this study, CAR-T cell therapy in patients with lupus was associated with normalization of key markers such as disease activity score, anti-DNA antibodies, urine protein, and C3 after a single treatment, with these improvements persisting for at least 24 months, essentially putting patients into remission. Similar benefits were reported for patients with myositis, with normalization of Muscle Testing scores and extra muscular symptoms. Again, in patients whose systemic sclerosis disease activity is down, and strikingly, in 6 months, the Rodnan skin score could improve dramatically.

> **The number of patients who will be treated with CD19 CAR-T cell therapy remains small, and therefore, conducting controlled studies will be difficult**

Comparing CD19 CAR-T cell therapy to Alexander the Great cutting the Gordian knot, Pillinger explained that you don't have to understand the subtleties of the way the knot is tied, whether it's a lupus knot or a myositis knot, whether it's a hemp knot or a cotton knot, he just cut right through it. That's similar to what CD19 CAR-T cell therapy does, it seems to "cut through" these complex diseases. However, he stressed that it is very time-consuming and costly. Furthermore, this therapy requires chemotherapy and may have long-term side

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effects that we are unaware of. Given these challenges, the number of patients who will be treated with CD19 CAR-T cell therapy remains small, and therefore, conducting controlled studies will be difficult.

## TWO DISEASES WITHOUT APPROVED TREATMENTS

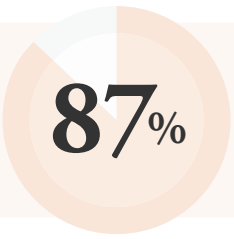
Whilst there are treatments that address the symptoms of Sjögren's syndrome, such as eye drops, there is currently no agent that targets the underlying biology of the disease. Pillinger explained that Sjögren's syndrome presents in various forms. There are systemic, more severe cases that clinicians "throw the kitchen sink at" with their approach to treatment options. There are also the more typical cases of Sjögren's syndrome, where patients are referred to as having a high symptom burden, dry eyes, fatigue, and pain. With the latter, Pillinger described how many clinicians have become somewhat nihilistic, assuming these symptoms will not respond to any treatment. However, this year, several studies have explored targeting the CD40 ligand co-stimulatory pathway and antigen presentation as a potential treatment for Sjögren's syndrome. One potential treatment is an antibody called iscalimab. This agent has been tested in both high-disease activity patients and high-symptom burden patients.[7]

> **"This marks the first randomized, double-blind, placebo-controlled trial for IgG4-related disease, and the results demonstrate significant efficacy"**

In both patient groups, iscalimab outperformed placebo. In particular, in the high symptom burden group, iscalimab improved fatigue and, strikingly, improved dryness, something that Pillinger admitted having long believed was untreatable. These findings suggest that targeting T cells through the CD40/CD40 ligand pathway may offer an effective approach to treating Sjögren's syndrome.

**PHASE III**

Enter this first serious Phase III clinical trial for IgG4 disease with inebilizumab, a monoclonal antibody that targets the same CD-19 on B cells as CD19 CAR-T cells.[8] In this trial, inebilizumab led to an 87% reduction in flare risk compared to placebo.



Finishing the session with research “ripped from the headlines”, Pillinger highlighted a breakthrough in the treatment of IgG4-related disease. Currently, there are no approved therapies for this condition, and patients often relapse with steroid treatment. Rituximab is another option, but robust supporting data is still lacking. Enter this first serious Phase III clinical trial for IgG4 disease with inebilizumab, a monoclonal antibody that targets the same CD-19 on B cells as CD19 CAR-T cells.[8] In this trial, inebilizumab led to an 87% reduction in flare risk compared to placebo. All key secondary endpoints were met, including reduced use of glucocorticoids. This marks the first randomized, double-blind, placebo-controlled trial for IgG4-related disease, and the results demonstrate significant efficacy.

> **We are embarking on an “extraordinary therapeutic adventure”, with many more remarkable developments to be expected in the coming years**

## CONCLUSION

The enlightening whirlwind tour of key research published in 2024 concluded with Pillinger reminding the audience that “the other 99% of important information” had been left out. He emphasized that his key takeaway from preparing for this session was that we are embarking on an “extraordinary therapeutic adventure”, with many more remarkable developments to be expected in the coming years. With apologies to Shakespeare, Pillinger closed by exclaiming, "O brave new world... that has such treatments in it!"

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