The Journey to Find the Right Treatment for Rheumatoid Arthritis

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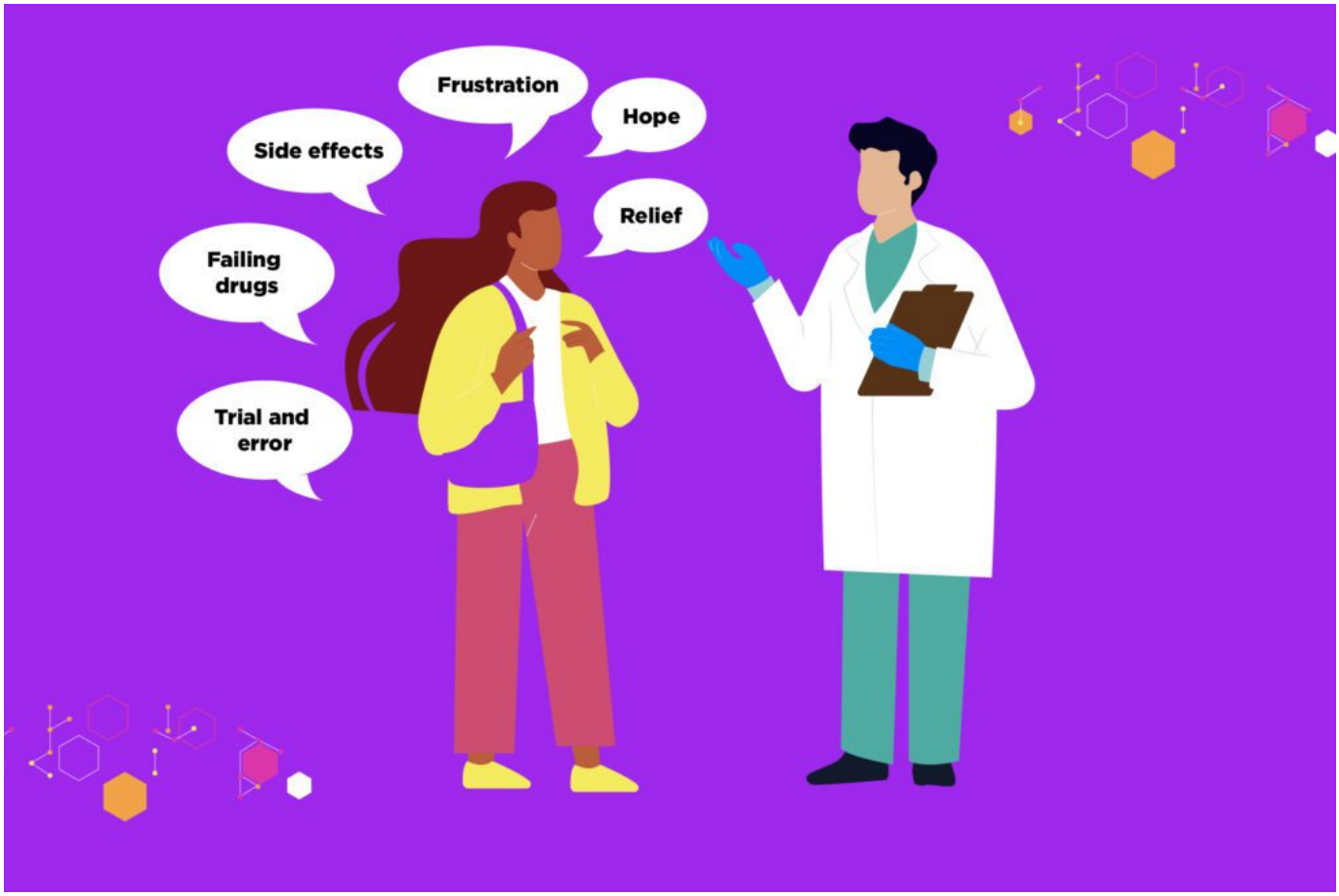
Rheumatologists and patients talk about the emotional process of trial and error as well as advances underway for landing on the right RA treatment sooner.

Check out "Your Guide to Precision and Personalized Medicine for Rheumatoid Arthritis" (https://precisionandpersonalizedmedicine.creakyjoints.org/)for more information on this topic.



(https://creakyjoints.org/wp-content/uploads/2022/10/The-Reality-of-RA-Treatment-nologo-1024x683.jpg)

Credit: Tatiana Ayazo

When Eliza M. Bates was first diagnosed with rheumatoid arthritis (RA), her doctor prescribed methotrexate (https://creakyjoints.org/treatment/methotrexate-myths/), a conventional synthetic disease anti-rheumatic modifying drug (DMARD). A few months later, he advised adding a tumor necrosis factor (TNF) inhibitor, another DMARD that is a biologic drug that he hoped would control Bates' still-active disease. But there are several TNF inhibitors, and there was no way to predict which one of them — if any — would help her.

“My doctor’s exact words were, ‘Have you seen any of the ads? Do you have a preference?’” says Bates, who was stunned to be asked to make that decision. She tried one drug which didn’t work for her and a few months later, she tried another which didn’t work for her either. Meanwhile, the first DMARD she had originally started taking was beginning to cause side effects.

“I was drinking milkshakes to try to keep weight on,” she recalls, adding that later in her RA journey she was placed on a steroid for some time which ended up making her gain 60 pounds.

Barely a year into her diagnosis at this point, Bates ended up going off the first DMARD and starting another two DMARDs, one of which was a different type of biologic DMARD known as a T-cell costimulatory blocking agent. “That combination actually worked pretty well for me until I decided I wanted to get pregnant,” she says. Her doctor then took her off those drugs, she went into a major flare, and that is where she was placed on steroids. After giving birth, a new round of trial and error ensued.

The current process of experimenting with a medication, waiting a few months to see how you fare, and then moving onto another drug that may or may not work for you is “extremely frustrating,” says Bates.

Understanding the Emotions

“It’s not just trial and error with your symptoms; it’s trial and error with your entire life,” says Bates. “If you flare, it might mean missing work or not being able to take care of your family. It’s a very disruptive process.”

Those who have been living with RA (https://creakyjoints.org/education/rheumatoid-arthritis-patient-guidelines/) are likely familiar with having to test out medication after medication before finding one that works. Even then, there are no guarantees, as some patients find that drugs that initially helped them eventually fail.

Seth Leibowitz was diagnosed with RA in 2008. The first DMARD he tried worked for three years and then he switched to a combination of DMARDs (anti-TNF combined with methotrexate) for five years. During this time, he was also on a steroid daily. After about five years, one of the DMARDs “wore off,” he said, so they tried a different DMARD which was a Janus kinase (JAK) inhibitor (https://creakyjoints.org/living-with-arthritis/treatment-and-care/medication/jak-inhibitor-safety-warnings-inflammatory-arthritis/).

“That didn’t work at all, and I actually got worse,” he recalls. “So we tried another DMARD. It was challenging as it was an injection as opposed to a subcutaneous pen. I did not like giving myself shots, and that lasted for only a few months. Finally, I gave in and decided to go back to the DMARD infusions, which I’m currently on.”

Making “Educated Guesses”

A person who is newly diagnosed with RA (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-patient-perspectives/managing-big-emotions-new-diagnosis-of-ra/) or unfamiliar with RA might be shocked to realize that these experiences are pretty normal. “At the beginning, I thought, ‘OK, I’ll get on medication, and everything will be fine,’ but it’s not like that,” says Bates. “I had no idea what to expect.”

Rheumatologists are equally frustrated by the situation, noting that although treatment guidelines, including those from the American College of Rheumatology (https://www.rheumatology.org/Portals/0/Files/2021-ACR-Guideline-for-Treatment-Rheumatoid-Arthritis-Early-View.pdf) (ACR), do provide some guidance, there are few iron-clad rules when it comes to properly treating RA in any given patient, says J. Eugene Huffstutter, MD, (https://www.arthritisassociateschatt.com/our-providers/j-eugene-huffstutter-md/) a rheumatologist with Arthritis Associates in Hixson, TN.

“If you’re lucky, the first drug you take works well and you maintain your normal lifestyle and activity. But sometimes it can take months or years before you figure out which medication is really tolerated by the patient and controls their RA the best,” he says.

Although no one has a crystal ball, rheumatologists do try to find some reason to pick one type of drug over another for a patient. They generally start with the DMARD, methotrexate, because it’s affordable and often effective by itself or when used in along with other medications; the ACR recommends it as the first-line

treatment for RA.

They also aim to get patients with an aggressive disease — as suggested by erosion on X-rays and positive autoantibody tests (https://creakyjoints.org/?s=ccp) — started on a different DMARD, usually a biologic as soon as possible. And they know that patients with underlying heart problems, for example, should generally avoid the JAK inhibitor DMARDs, and that those with interstitial lung disease should usually be treated with the DMARD rituximab (Rituxan), which focuses on depleting B cells.

Beyond that, "what we do is make educated guesses," says rheumatologist Isabelle Amigues, MD, (https://www.nationaljewish.org/doctors-departments/providers/physicians/isabelle-amigues) Assistant Professor at National Jewish Health in Denver, CO.

To further complicate matters, rheumatologists usually have to follow specific insurer-mandated protocols. That often starts with a request for prior authorization to obtain coverage for a costly biologic. It also frequently entails a process called step therapy, in which an insurer requires that a patient try and fail a certain drug or drugs before they will agree to pay for the treatment the patient and their doctor actually want.

Research (https://pubmed.ncbi.nlm.nih.gov/27654603/) has shown, for instance, that patients who fail on TNF inhibitor DMARDs are more likely to reach low or moderate disease activity faster if they switch to drug in a different class of DMARDs—perhaps an interleukin-6 (IL-6) inhibitor like tocilizumab (Actemra) or a JAK inhibitor like baricitinib (Olumiant)—rather than trying out a different TNF inhibitor DMARD. But that's not always possible.

"If insurance is not making me do what they want, I'd *not* go to a second TNF inhibitor" after a patient failed a first one, says Amigues. Yet she's often forced to go against her preference in order to get the medication covered.

"In the long-term, the cheapest drug is the most effective one, the one that really controls someone's disease," says Huffstutter, noting that insurance companies can be short-sighted. At the same time, it can be hard to argue that a specific drug is best for a patient when they haven't yet tried it. Recent advancements, however, might change that.

Precision Medicine: The End of Trial-and-Error?

Today RA is treated as a singular condition, yet in reality there are likely numerous sub-types that are driven by different cytokines (inflammatory proteins), says Huffstutter. If scientists could identify which patients are in a given group, they might be able to figure out who should take a certain medication before they even try it.

That's exactly the idea behind precision medicine, which aims to tailor treatment by homing in on a patient's genetic or molecular characteristics. Precision medicine has already transformed cancer treatment, and patients are now routinely treated based on the biology of their tumor. Rheumatologists hope that the RA will one day be able to be treated similarly.

The field is already on its way with the introduction of PrismRA, a first-of-its-kind blood test that analyzes 23 distinct biological features including 19 gene expression features and 4 clinical and laboratory measures and uses that information from a patient's blood sample to help guide targeted treatment decisions in rheumatoid arthritis. Research has found that this test can predict with 90 percent accuracy (https://www.prismra.com/about-prismra/faq/) who will *not* respond to TNF inhibitor DMARD therapies with a test result of inadequate response and would therefore be better off choosing a different type of medication.

PrismRA is the only commercially available molecular signature response classifier test to predict non-response to TNF inhibitor DMARDs. The company is also working to launch a version of the test that predicts response (instead of non-response) to the drug as well as a test for T-cell and Jaki classifiers and IL-6.

Meanwhile, other scientists across the U.S. (https://www.medicine.northwestern.edu/divisions/rheumatology/research/reason.html) are conducting research involving joint tissue biopsies: They are taking small samples of joint tissue from RA patients who are beginning

any new RA treatment and again six weeks later and doing genetic sequencing on these samples. The eventual goal is to create genetic signatures based on joint tissue biopsies and use them to match a patient to the best therapy for them. It will likely be three to five years before this research is completed, says Harris Perlman, PhD, (https://www.feinberg.northwestern.edu/faculty-profiles/az/profile.html?xid=12783) who is heading up this work at Northwestern University.

Any advancements in precision medicine for RA will likely be welcomed by both patients and providers. As physicians, “we don’t want to spend several months putting a patient on an expensive therapy that’s not likely to help them while exposing them to toxicity issues along the way,” says Huffstutter.

This article is part of “Your Guide to Precision and Personalized Medicine for Rheumatoid Arthritis” and was made possible with support from Scipher Medicine.

+ Sources

Suggested Reading

What I Lost (And Now Gained) Because of Rheumatoid Arthritis (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-patient-perspectives/what-i-lost-and-gained-from-ra/)

Personalizing Your Rheumatoid Arthritis Treatment: 5 Questions to Ask Your Doctor (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-treatment/personalizing-ra-treatment-questions-to-ask-doc/)

Infographic: What Do Rheumatoid Arthritis Patients Know About Precision Medicine, Flares, and Remission? (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-treatment/infographic-precision-medicine-flares-and-remission/)

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What I Lost (And Now Gained) Because of Rheumatoid Arthritis (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-patient-perspectives/what-i-lost-and-gained-from-ra/)

Osteoporosis and Mental Health: What You Need to Know (https://creakyjoints.org/comorbid-conditions/osteoporosis-and-mental-health-what-you-need-to-know/)

How to Protect Yourself Against COVID-19 During the 2022 Holiday Season (https://creakyjoints.org/living-with-arthritis/coronavirus/managing-symptoms/how-to-protect-against-covid-holiday-2022/)