Interrupting immunomodulators for infection: a strategy without evidence?

Written by The Life Science Feed Editorial Team · Published 6 August 2026 · Edited by Mara Voss

For decades, clinicians have advised patients with inflammatory rheumatic diseases (IRDs) to temporarily interrupt their immunomodulatory agents (IAs) when an infection strikes. This practice, enshrined in many guidelines, aims to prevent infection exacerbation. But the evidence supporting this widespread recommendation has been surprisingly thin, leaving many to wonder if it truly benefits patients or merely complicates their care. A new randomized controlled trial, published in Clinical Infectious Diseases, directly challenged this conventional wisdom, comparing continuation versus temporary interruption of IAs during infections. The findings suggest that the long-held advice may be unnecessary, and potentially even detrimental, for many patients.

KEY TAKEAWAYS

- The Pivot: Continuing immunomodulatory agents during infection in IRD patients is non-inferior to temporary interruption for preventing severe infection.
- The Data: The primary outcome of severe infection or treatment failure occurred in 14.3% of the continuation group vs 17.3% of the interruption group (HR 0.81; 95% CI, 0.53-1.24; P=.33).
- The Action: Clinicians should reconsider the routine recommendation to interrupt immunomodulatory agents during mild-to-moderate infections in patients with inflammatory rheumatic diseases.

Patients living with inflammatory rheumatic diseases often rely on immunomodulatory agents to control their underlying autoimmune conditions. These therapies, which include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), suppress immune responses to mitigate inflammation and prevent joint damage. But this immune suppression carries an inherent risk: an increased susceptibility to infections. The prevailing clinical wisdom, therefore, has been to temporarily halt these agents during an active infection, a strategy intended to allow the immune system to mount a more robust defense. This practice, however, lacks robust evidence from randomized controlled trials, relying instead on expert opinion and observational data.1

The CONTINUUM trial, led by Opdam and colleagues, directly addressed this clinical uncertainty. The investigators enrolled 600 adult patients with inflammatory rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis, who were receiving stable doses of immunomodulatory agents. Patients were recruited from 12 centers in the Netherlands and randomized 1:1 to either continue their IA or temporarily interrupt it for 7 days upon experiencing a new infection. The study focused on mild-to-moderate infections, such as upper respiratory tract infections, urinary

tract infections, and skin infections, which are common occurrences in this patient population. The primary endpoint was a composite of severe infection or treatment failure within 28 days of randomization. Treatment failure was defined as either an infection-related hospitalization, an infection requiring intravenous antibiotics, or a worsening of the underlying rheumatic disease.1

The Trial's Design and Patient Cohort

The CONTINUUM trial was an open-label, multicenter, randomized controlled non-inferiority trial. Patients were eligible if they were 18 years or older, had a confirmed diagnosis of an IRD, and were on a stable dose of a csDMARD, bDMARD, or tsDMARD for at least 3 months. The study excluded patients with severe infections at baseline, those requiring immediate hospitalization, or those with a history of recurrent severe infections. The mean age of the participants was 61 years, and 65% were female. Rheumatoid arthritis was the most common diagnosis, affecting 55% of the cohort, followed by psoriatic arthritis (20%) and spondyloarthritis (15%). The remaining 10% comprised other IRDs. The most frequently used immunomodulatory agents were methotrexate (40%), adalimumab (25%), and etanercept (15%). Patients were followed for 28 days after randomization, with safety and efficacy assessments conducted at regular intervals.1

The randomization process ensured a balanced distribution of baseline characteristics between the two groups. Patients in the interruption group were instructed to stop their IA for 7 days, or until the infection resolved, whichever came first. They were advised to restart their medication after this period. The continuation group maintained their regular IA regimen. Both groups received standard care for their infection, including antibiotics if clinically indicated. The study's non-inferiority margin for the primary outcome was set at 5%, meaning that if the upper bound of the 95% confidence interval for the hazard ratio did not exceed 1.25, continuation would be considered non-inferior to interruption. This margin was chosen based on clinical consensus regarding an acceptable difference in outcomes.1

Primary and Secondary Outcomes

The primary outcome, a composite of severe infection or treatment failure within 28 days, occurred in 14.3% (43/300) of patients in the continuation group and 17.3% (52/300) of patients in the interruption group. The hazard ratio for this outcome was 0.81 (95% CI, 0.53-1.24; P=.33). This result demonstrated that continuing immunomodulatory agents was non-inferior to temporarily interrupting them, as the upper bound of the confidence interval (1.24) did not cross the pre-specified non-inferiority margin of 1.25. The difference between the groups was not statistically significant, indicating no clear benefit for interruption.1

Breaking down the composite endpoint, severe infections occurred in 8.7% (26/300) of the continuation group versus 10.3% (31/300) of the interruption group. Treatment failure, defined as infection-related hospitalization, IV antibiotics, or rheumatic disease flare, occurred in 9.3% (28/300) of the continuation group and 11.7% (35/300) of the interruption group. Neither component showed a statistically significant difference between the two strategies. This suggests that the perceived benefit of interruption in reducing infection severity or progression may not be realized in practice.1

Secondary outcomes provided further insights. The duration of infection symptoms was similar between the groups, with a median of 7 days in both (P=.68). The time to resolution of infection was also comparable. Importantly, the study also tracked flares of the underlying rheumatic disease. Disease flares occurred in 6.0% (18/300) of patients in the continuation group compared to 9.7% (29/300) in the interruption group. While not statistically significant (P=.07),

this trend suggests that interrupting IAs might actually increase the risk of disease exacerbation, potentially leading to more discomfort and requiring additional interventions for patients. This finding, if confirmed in larger studies, could significantly shift clinical practice.1

Safety and Subgroup Analyses

Safety outcomes were closely monitored. Adverse events were reported in 35% of the continuation group and 38% of the interruption group, with no significant differences in the types or severity of events. The most common adverse events were gastrointestinal disturbances and skin reactions, consistent with the known side effect profiles of the immunomodulatory agents. No unexpected safety signals emerged from either treatment arm. This reinforces the idea that continuing these agents during infection does not appear to introduce new or increased safety risks.1

Subgroup analyses were conducted based on the type of immunomodulatory agent (csDMARDs vs bDMARDs/tsDMARDs), type of IRD, and age. No significant interactions were found, meaning the effect of continuation versus interruption was consistent across these subgroups. This broad applicability is crucial, as it suggests the findings are relevant to a wide range of patients with IRDs, regardless of their specific diagnosis or the class of immunomodulatory agent they are receiving. The study did not, however, specifically analyze patients on high-dose corticosteroids, which are known to significantly increase infection risk. This remains an area for further investigation.1

Where the Evidence Falls Short

The open-label design is the obvious caveat. While objective endpoints like hospitalization for severe infection are less susceptible to bias, patient-reported outcomes and clinician assessments of infection severity or disease flare could be influenced by knowledge of the treatment assignment. A double-blind design would have strengthened the evidence, but blinding in a trial involving medication interruption is inherently challenging. Still, the primary outcome was a hard endpoint, mitigating some of this concern.1

The trial was also not powered to detect differences in rare but serious infections, such as opportunistic infections, which are a concern with some immunomodulatory agents. The focus was on common, mild-to-moderate infections, which represent the vast majority of infectious episodes in this population. Whether these findings extend to more severe or unusual infections remains unclear. The 28-day follow-up period, while sufficient for acute infection outcomes, might not capture longer-term consequences of either strategy, such as cumulative infection burden or sustained disease control. Future research with longer follow-up periods could provide a more complete picture. Clinicians looking for a comprehensive guide to managing such complex patients may find the Oxford Handbook of Rheumatology a useful resource.

Finally, the study population was primarily from the Netherlands, a country with a well-developed healthcare system and specific prescribing patterns. While the general principles of IRD management are similar across Europe, variations in local guidelines, access to care, and patient demographics could influence the generalizability of these findings. However, the biological mechanisms underlying IRDs and infection responses are universal, suggesting the core findings are likely broadly applicable.1

CLINICAL IMPLICATIONS

> The CONTINUUM trial delivers a clear message: the routine interruption of immunomodulatory agents during mild-to-moderate infections in IRD patients offers no discernible benefit in preventing severe infection or treatment failure. This challenges a long-standing clinical practice that has often caused unnecessary anxiety for patients and complicated medication adherence. Clinicians should now feel confident in advising many of their IRD patients to continue their prescribed therapies, even when facing a common infection.
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> This shift in practice could significantly improve patient quality of life by reducing the risk of disease flares, which the study hinted might be more common with interruption. Avoiding flares means fewer clinic visits, less pain, and a more stable disease course. It also simplifies medication management, removing a common barrier to consistent adherence.
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> For guideline bodies, these data provide a strong impetus to review and revise current recommendations. The evidence base for interruption was always weak, and now a randomized trial directly refutes its utility for common infections. This is a pragmatic finding that should translate directly into updated clinical guidance, streamlining care for a large patient population.
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> The pharmaceutical industry, particularly manufacturers of bDMARDs and tsDMARDs, may also see this as an opportunity to reinforce the safety and stability of their products. Reassuring patients that their essential medication can be continued during minor infections could enhance trust and adherence, ultimately benefiting both patients and prescribers.

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REFERENCES

1. 1. Opdam MAA, den Broeder N, van Crevel R. Continuation Versus Temporary Interruption of Immunomodulatory Agents During Infections in Patients With Inflammatory Rheumatic Diseases: A Randomized Controlled Trial. Clin Infect Dis. 2026.

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