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EDITORIAL

The ADJUST trial and its implications for biologic discontinuation in juvenile idiopathic arthritis-associated uveitis

Eye; https://doi.org/10.1038/s41433-025-04208-z

Juvenile idiopathic arthritis-associated uveitis (JIA-U) represents nearly half of pediatric uveitis cases and remains a leading cause of preventable childhood blindness. The introduction of biologic therapies, particularly the tumor necrosis factor inhibitor adalimumab, has transformed disease control for patients with persistent or refractory inflammation. Treatment discontinuation guidelines vary internationally (18 months in NHS England versus 2 years in ACR/SHARE recommendations), yet all rely primarily on retrospective data with acknowledged limitations [1–3]. The ADJUST trial, a multicentre RCT reported in the Lancet, addressed this evidence gap by randomizing 87 patients with at least 12 months of controlled JIA-U across three countries to continue adalimumab or receive matched placebo for 48 weeks [4]. Treatment failure was defined by recurrence of ocular inflammation or arthritis requiring unmasking, with stable baseline DMARDs and topical corticosteroids maintained throughout.

The trial demonstrated that patients who discontinued adalimumab had significantly shorter time to treatment failure compared with those who continued, with 68% experiencing relapse within 48 weeks. Most failures occurred within six months and were primarily due to uveitis recurrence rather than arthritis. Importantly, all patients who relapsed successfully regained disease control upon restarting adalimumab. Despite the desire to reduce long-term immunosuppression due to concerns about side effects, infections, and cost, this study suggested that ongoing treatment may be necessary to maintain disease control and protect vision. Unexpectedly, concomitant DMARDs provided no protection against relapse despite their association with lower anti-adalimumab antibody concentrations and potentially higher adalimumab drug levels, suggesting that the immunological mechanisms underlying relapse are more complex than simple drug immunogenicity.

The ADJUST trial challenges current discontinuation guidelines and raises several key questions for clinicians and policymakers:

WHEN SHOULD WE STOP BIOLOGIC THERAPY IN UVEITIS?

We enrolled patients after achieving at least one year of controlled uveitis, reflecting the absence of robust evidence defining a safe duration of inactivity before treatment withdrawal. Despite this, relapse remained common, even among the 71% of participants who had maintained disease quiescence for more than two years. Subgroup analysis demonstrated that extending the period of prior control did not reduce the risk of recurrence, suggesting that sustained remission off treatment cannot be reliably predicted by duration of inactivity alone. These findings align with previous observational studies, which similarly report high relapse rates following biologic tapering or cessation, underscoring the continued uncertainty around when it is safe to discontinue therapy [5]. At present, decisions to withdraw should be individualized, guided by the risk of visual loss, previous relapse history, and patient preference, with intensive ophthalmic follow-up during the first six months after withdrawal until validated biomarkers can define which patients can safely discontinue treatment.

WHY MUST UVEITIS BE TREATED LONGER THAN OTHER IMMUNE-MEDIATED INFLAMMATORY DISEASES (IMIDS)?

Across pediatric and adult IMIDs, randomized withdrawal designs typically report relapse rates in the range of roughly 30–50% by about one year. By contrast, in ADJUST, stopping adalimumab led to 68% treatment failure within forty-eight weeks, the majority driven by uveitis rather than arthritis, and most occurring within the first six months after withdrawal. This pattern suggests a disease- and tissue-specific vulnerability in the ocular environment. A key contributing factor is the persistence of tissue-resident immune populations within the uveal tract, including memory T cells that remain locally primed despite clinical quiescence and can rapidly reactivate in response to local cytokine or danger signals once systemic TNF inhibition is withdrawn. The heightened sensitivity of ophthalmic outcome measures, such as Standardization of Uveitis Nomenclature anterior chamber cell grading [6], means that even subtle inflammatory changes mandate intervention, whereas many rheumatology and dermatology withdrawal trials use broader composite indices or require confirmation over multiple visits, leading to lower apparent recurrence rates even when subclinical disease activity persists. Other contributory mechanisms may include the interplay among TNF-α, IL-6, and IL-17–driven pathways, which together sustain ocular inflammation. Withdrawal of TNF inhibition may disrupt this balance, allowing compensatory cytokine networks to reactivate within the eye and rapidly rekindle disease activity.

IS THERE A WINDOW OF OPPORTUNITY TO "SWITCH DISEASE OFF"?

The concept of a "window of opportunity"—a critical early period during which intensive immunomodulation might alter disease trajectory—has been established most clearly in rheumatoid arthritis, where early biologic or combination therapy improves the likelihood of sustained remission and reduces structural damage. Whether a comparable window exists in uveitis, however, remains unproven. In JIA-U, earlier introduction of biologics such as adalimumab has been associated with faster and more complete suppression of inflammation, fewer relapses, and reduced cumulative corticosteroid exposure. Nevertheless, current evidence does not yet demonstrate that early

Received: 26 October 2025 Revised: 5 December 2025 Accepted: 19 December 2025
Published online: 08 January 2026

intervention induces durable immune tolerance once therapy is withdrawn. Future biomarker-driven analyses from the ADJUST trial aim to identify predictors of sustained remission, including the MRP8/14 complex, systemic inflammatory markers, and peripheral blood transcriptomic and gut microbiome profiles. These studies will, we hope, bring us closer to understanding which patients can safely step away from treatment without risking sight-threatening relapse.

FINALLY, SHOULD ANTI-TNF THERAPY NOW BE CONSIDERED FIRST-LINE IN JIA-U?

Historically, treatment algorithms favored methotrexate as the initial systemic agent because of its lower price, oral route, and long experience of use, reserving biologics for refractory disease. However, this cost-based hierarchy is eroding. With biosimilar adalimumab now widely available, the economic argument for delay is weaker, and the clinical rationale for earlier biologic intervention is strengthening—particularly in sight-threatening uveitis where irreversible damage can occur before methotrexate becomes effective. Mechanistically, TNF sits upstream of multiple inflammatory cascades implicated in uveitis, and early blockade may therefore interrupt disease propagation more effectively than targeting downstream pathways. Clinically, adalimumab achieves faster and more sustained quiescence than conventional DMARDs such as methotrexate, as demonstrated in the ADVISE trial, where corticosteroid-sparing success and complete disease control were achieved in a higher proportion of patients receiving adalimumab [7]. Finally, as real-world experience expands, the safety margin for pediatric and adolescent use has become increasingly reassuring, narrowing the historical risk gap between methotrexate and biologic agents. As biologics become more affordable, the conversation will move from “when do we escalate?” to “why wait at all?”.

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AUTHOR CONTRIBUTIONS

AVR and PM co-authored the article and approved the final version of the manuscript. NRA edited and approved the final version of the manuscript.

COMPETING INTERESTS

The authors have no conflicts of interest to declare. PM is a member of the Eye editorial board. NRA has been an advisor to Roche.

ADDITIONAL INFORMATION

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