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Therapeutic drug monitoring for immune mediated inflammatory diseases

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Low certainty evidence suggests a proactive approach during maintenance therapy for patients treated with infliximab

About 1% of adults and children globally,[1] and between 5% and 7% of those living in western societies,[2] have a chronic immune mediated inflammatory condition. Infliximab and adalimumab, which are anti-tumour necrosis factor (TNF) treatments, are the most widely used biologics for treating immune mediated inflammatory disorders. These disorders include inflammatory bowel disease, inflammatory arthritis (psoriatic arthritis, rheumatoid arthritis, and spondyloarthritis), and psoriasis. In 2023, anti-TNF treatments accounted for a global expenditure of US$43bn (£33bn; €40bn).[3]

About one third of patients lose response to anti-TNF treatment.[4–6] For patients with inflammatory bowel disease and rheumatoid arthritis, compared with empirical dosing alone, anti-TNF therapeutic drug monitoring could improve efficacy, drug persistence, and safety, and might be more cost effective.[7–9] However, debate remains as to whether such monitoring should be performed for patients with other inflammatory conditions and the optimal timing.

Proactive versus reactive therapeutic drug monitoring

Proactive therapeutic drug monitoring is the routine measurement of drug and anti-drug antibody concentrations, irrespective of a patient's clinical status. In reactive therapeutic drug monitoring, drug and anti-drug antibody concentrations are measured in response to a disease flare or loss of response to treatment. In a linked systematic review and meta-analysis of 10 randomised controlled trials, Zeraatkar and colleagues (doi:10.1136/bmjmed-2024-000998)[10] report the efficacy and safety of proactive therapeutic drug monitoring versus standard of care (no or reactive therapeutic drug monitoring) for 2383 people with inflammatory bowel disease, inflammatory arthritis, or psoriasis treated with anti-TNF treatments using GRADE (grading of recommendations assessment, development and evaluation).

Based on low certainty evidence, patients treated with infliximab who had proactive therapeutic drug monitoring during maintenance treatment were more likely to have sustained disease control or be in remission than those receiving standard care (absolute risk difference 146 per 1000 patients treated for one year (95% confidence interval 78 to 224)). This finding means that for every 100 people treated with infliximab who received proactive therapeutic drug monitoring, 15 additional people will have sustained control of their disease or be in remission compared with standard care.

In patients treated with adalimumab maintenance treatment, the review found very low certainty evidence for the effect of proactive therapeutic drug monitoring on sustained disease control or remission. The authors found no evidence for an effect of proactive therapeutic drug monitoring during the induction phase with infliximab treatment, and no trials assessed therapeutic drug monitoring during induction with adalimumab. Rates of adverse events in either testing arm were no different by drug or phase of treatment, although certainty of evidence was very low due to risk of bias, imprecision, or indirectness.

Distinct and novel findings

This review was performed by the MAGIC Evidence Ecosystem Foundation (magicevidence.org), a non-profit research team of methodologists, clinical researchers, and patients. It forms the basis of the copublished BMJ Rapid Recommendations clinical practice guideline.[11] A strength of the authors' approach was the steps taken to reduce bias from financial and intellectual conflicts of interest—the authors are not specialists in therapeutic drug monitoring, nor did they declare any relevant conflicts of interest.

In the context of two previous meta-analyses comparing therapeutic drug monitoring with standard care in patients with inflammatory bowel disease treated with anti-TNF, Zeraatkar and colleagues' results are distinct and novel additions to the evidence base. In one meta-analysis of nine randomised controlled trials including 1405 patients that also used GRADE, during assessment of maintenance treatment only, no benefit of proactive therapeutic drug monitoring compared with standard care was seen for achieving or maintaining clinical remission for patients treated with infliximab or adalimumab.[12] A subsequent meta-analysis updated the search to include 17 cohort studies (in addition to the nine trials), expanded outcomes of interest but combined induction and maintenance phases of treatment, and grouped anti-TNF treatments together.[13] It concluded that proactive therapeutic drug monitoring, compared with reactive testing, was associated with significant reduction in treatment failure and reduction in hospital admission rates. To the best of our knowledge, no trials or meta-analyses answering this research question have been performed in patients with inflammatory arthritis or

psoriasis, making Zeraatkar and colleagues' review a timely one.

In alignment with GRADE, the choice of outcomes in Zeraatkar and colleagues' review was focused on patients' subjective experience, inclusive of typical clinical endpoints (disease control and remission), safety (adverse events and development of anti-TNF antibodies), and patient reported outcomes (quality of life, physical function, and mental health). Despite being associated with a lower risk of clinical relapse,[14] endoscopic remission for patients with inflammatory bowel disease was intentionally excluded because it did not reflect patients' subjective experience. Outcomes of particular importance to patients across all conditions, work or school absenteeism and disability, could not be analysed because of lack of evidence.

Pooling of patients

A decision taken in Zeraatkar and colleagues' review that is likely to spark discussion is the pooling of patients with inflammatory bowel disease, inflammatory arthritis, and psoriasis. The authors adopted this approach having followed the updated GRADE guidance,[15] and concluded that the best available evidence suggests that the effects of therapeutic drug monitoring are consistent across these disease groups. More randomised controlled trials in immune mediated inflammatory conditions (excluding inflammatory bowel disease) are needed to test this assumption robustly, but this review[10] and guideline[11] provide a basic framework across which different disease group's protocols for therapeutic drug monitoring can be compared.

Of 2327 patients in the review who had specific inflammatory disease reported, two thirds had inflammatory bowel disease (1571 (67.5%)), and the remaining third had four immune mediated inflammatory disorders (258 (11.1%) rheumatoid arthritis, 347 (14.9%) spondyloarthritis, 92 (4.0%) psoriatic arthritis, and 59 (2.5%) psoriasis). All patients without inflammatory bowel disease were recruited to the Norwegian Drug Monitoring study,[16 17] which was underpowered to test for effectiveness of therapeutic drug monitoring across different disease groups. To overcome this, the authors did sensitivity analyses using interaction testing, and found no difference in the effect of proactive therapeutic drug monitoring versus standard care across different disease groups or between studies with high and lower risk of bias.

The authors acknowledge, however, limited data, selection bias towards including patients with inflammatory bowel disease, and imprecision as important caveats. As a result, they downgraded the certainty of evidence of all three of their key recommendations in the linked clinical practice guideline owing to serious concerns with indirectness, and acknowledged the need to update their guideline as new data emerges.[11] The pooling of effect of proactive therapeutic drug monitoring across immune mediated inflammatory disorders challenges our understanding of these disease groups as separate entities with different immunopathogenesis, background patient characteristics, and differences in response to testing and treatment.

Whether to measure therapeutic drug monitoring proactively or reactively is only one piece of a difficult puzzle. In clinical practice, patients at higher risk of anti-TNF treatment failure, including those who smoke, have higher body mass index, and have severe inflammation,[4 18 19] are more likely to receive either form of therapeutic drug monitoring frequently with the aim of optimising treatment early to prevent poor clinical outcomes. How best to minimise inconvenience to patients and make better use of healthcare resources remains uncertain. As patients begin to transition from intravenous to subcutaneous infliximab, and with increased use of telemedicine, patient-led remote intracapillary blood sampling for therapeutic drug monitoring could be part of the solution.[20] Future studies should aim to understand the independent effect of proactive versus reactive therapeutic drug monitoring on patient centred outcomes in separate disease groups, the usefulness of either approach in predicting long term clinical outcomes beyond one year, and the cost effectiveness in the era of biosimilar preparations.

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