8. b/tsDMARD Dose Reduction and Discontinuation strategies

8.1 Rheumatoid Arthritis: Dose reduction or discontinuation of biologic or targeted synthetic DMARDs

Background: Rheumatoid arthritis (RA) causes swollen, stiff and painful joints, when the immune system - which normally fights infection - attacks the lining of joints. There is no cure for RA, so treatments aim to relieve pain and stiffness, improve ability to move, and prevent damage to the joints.

The cornerstone of pharmacologic treatment for rheumatoid arthritis is disease-modifying anti-rheumatic drugs (DMARDs), which control the inflammation and thus symptoms and prevent joint damage. DMARDs can be categorised according to their structure and mechanisms of action. Conventional synthetic DMARDs (csDMARDs), such as methotrexate, sulfasalazine and hydroxychloroquine do not target a specific molecular structure. Conversely, targeted synthetic DMARDs (tsDMARDs), such as tofacitinib and baricitinib, are a newer class of medications, designed to act on a specific molecular target. Biologic DMARDs (bDMARDs) are derived biologically, and similarly to tsDMARDs, were designed to target specific cells or proteins involved in the inflammatory response present in RA. Given these are biologically derived proteins, it is impossible to exactly reproduce their complex structure. Therefore, biologic DMARDs can be further classified into bio-originator and biosimilar DMARDs, to specify whether they were made by the first or subsequent manufacturers.

The newer tsDMARDs and bDMARDs are more costly than csDMARDs, and it is unclear if they are more effective. However, as successful treatment, in particular combination treatment, often leads to low disease activity and even remission of disease in some people, to prevent over-treatment, an optimal dose of DMARDs is often sought in the individual patient, which is the lowest dose that maintains the targeted low disease activity state. This process of dose optimisation often involves dose reduction (or cessation) after the clinical target is reached. This is often referred to as ‘down-titration’. This might reduce dose-dependent side effects (mainly infections) and costs and could involve any type of DMARD.

The best strategies for down-titration are not known. Possible strategies include:

1. down-titration to either lower dose (e.g., 50mg etanercept once weekly reduced to 25mg once weekly) or an increased interval between doses (e.g., 50mg etanercept once a week reduced to 50mg once every two weeks) which is then the new maintenance dose;
2. stepwise down-titration similar to 1) but according to disease activity (disease activity-guided dose reduction); or
3. simply discontinuing the medication.

Executive Summary - bDMARD or tsDMARD down-titration (dose reduction including disease activity-guided dose reduction, or discontinuation) in adults with RA, with low disease activity or remission:

Compared to continuation of treatment at the standard dose, dose reduction of bDMARDs (mainly anti-TNFs, but with some data on B-lymphocyte, T-lymphocyte and interleukin-6 inhibitors) or tsDMARDs in participants with low disease activity for 3-12 months:

- Is comparable in terms of mean disease activity and function;
- Is probably comparable in terms of proportion of participants with persistent remission, proportion with a flare, quality of life and number of serious adverse events;
- May be comparable in terms of proportion who switch to another treatment, disease progression as measured by proportion with minimal radiographic damage, and number of withdrawals due to adverse events.

Compared to continuation of treatment at the standard dose, discontinuation of bDMARDs (evidence was only available for anti-TNFs for this question) in participants with low disease activity for 3-12 months:

- Is probably slightly inferior to continuation of treatment in terms of mean disease activity;
- May be inferior with respect to the proportion of participants with persistent remission, proportion with a flare disease progression, disease progression as measured by proportion with minimal radiographic damage, function and quality of life.

We are uncertain if the number of serious adverse events and the number of withdrawals due to adverse events differs with discontinuation compared to continuation, as there were too few events to estimate this with certainty. Furthermore, no studies reported on the number of participants who switched treatments.

Abbreviations used in this recommendation:

- bDMARDs - biological disease-modifying antirheumatic drugs (DMARDs), including TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab), IL-6 inhibitors (tocilizumab), T-cell costimulatory signal inhibitor (abatacept), B-cell inhibitors (rituximab)
- tsDMARDs - targeted synthetic DMARDs, including Janus Kinase inhibitors (eg tofacitinib, baricitinib)
- b/tsDMARDs - either bDMARDs or tsDMARDs
- csDMARDs - conventional synthetic DMARDs (e.g. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine)