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Original Article

Can rheumatoid arthritis ever cease to exist: a review of various therapeutic modalities to maintain drug-free remission?

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Abstract: Therapies for rheumatoid arthritis (RA) were mostly aimed at reducing the pain, stiffness and further progression of joint destruction. However, with the advent of biologic agents that act against specific inflammatory cytokines contributing to RA pathogenesis (treat-to-target strategy), the degree of remission achieved has been remarkably impressive. In particular, inhibition of tumor necrosis factor α (TNFα), interleukins-1 and -6 and receptor-activator of nuclear kappa B ligand by neutralizing antibodies in early diagnosed RA patients has resulted in lowering of disease activity to levels that enable them to function as in the pre-disease stage. There are other biologic approaches such as depletion of B cells and blocking T-cell co-stimulators that have been included successfully in RA therapy under the class of disease-modifying anti-rheumatic drugs (DMARD). Given the excellent clinical outcomes of biologic DMARDs when initiated early in RA, discontinuation or dose tapering is practised. Because biologic DMARDs are expensive and also known to make users vulnerable to viral infections, dose reduction and drug holiday are reasonable steps when sustained good clinical response has been achieved. Majority clinical studies have been done with TNF inhibitors and data suggest that sustained remission of RA is achieved in several multi-centric studies carried out worldwide. However, high flare rate and reappearance of disease has been reported in several cases. This review critically discusses response predictors of biologic DMARDs, the case for treatment relaxation, strategizing drug tapering considering patient eligibility and timing in light of available clinical practice guidelines of RA.

Keywords: Biologic agents, withdrawal, remission, disease activity score, therapeutics, joint destruction

Introduction

Rheumatoid arthritis (RA) is an immune-mediated systemic inflammatory disease that affects the joints to cause polyarthritis due to the destruction of cartilage and bone. Focal marginal articular erosions, subchondral bone loss, periarticular osteopenia and systemic osteoporosis are four pathologic stages of skeletal remodelling that characterize RA. The focal marginal erosion is a radiologic feature for RA. These erosion sites on histologic examination display inflamed synovial tissue attached to the bone surface to form a covering called pannus. The space between the pannus and adjacent bone is lined with osteoclasts which cause focal bone resorption. The endosteal surface of the subchondral bone also undergoes focal resorption due to RA and results in joint destruction. Histologic examination show that bone marrow adjacent to subchondral bone has a fibrovascular stroma invaded by inflammatory cells and is strongly predictive of the subsequent development of local bone erosions at these sites by adversely affecting bone remodelling [1, 2]. Indeed, magnetic resonance imaging showed edema in the bone marrow of RA patients which corroborates histologic findings of lesions [3]. Supporting evidence regarding the role of osteoclasts in the pathogenesis of focal articular bone loss has come from transgenic mouse experiments. Mice lacking genes of two potent osteoclastogenic cytokines such as tumor necrosis factor α (TNFα) or receptor

activator of nuclear kappa B ligand (RANKL) were resistant to the induction of inflammatory arthritis as evidenced from absence of focal articular bone resorption despite the presence of significant synovial inflammation [4-6]. TNFα causes increased production of RANKL from the activated T-lymphocytes, which is the most potent osteoclastogenic cytokine. In studies on a cohort of patients with RA followed up for 11 years have reported higher circulating RANKL as a predictor of generalized bone loss [7, 8]. Suppression of TNF mitigated osteoporosis by inhibiting circulating RANKL in RA patients [9]. Moreover, denosumab a fully human monoclonal antibody to RANKL when co-administered with methotrexate was found to significantly inhibit progression of bone erosion in Japanese patients with RA at 12 months compared with control (methotrexate alone) [10], which confirmed that RANKL was the execution arm of bone loss in RA. Despite a central pathophysiological role of RANKL in RA, the approach to inhibit the action of this cytokines is not a mainstream clinical management strategy.

Coupled with increased bone loss, bone repair is non-existent in focal marginal and subchondral bone loss conditions likely due to the increased production of dickkopf-related protein 1 (DKK-1), an inhibitor of the Wnt pathway by synovial fibroblasts, endothelial cells and chondrocytes due to the action of TNFα. Because the Wnt pathway has a crucial role in osteoblast-mediated bone formation, increased production of endogenous Wnt antagonist such as DKK-1 has a negative effect on bone repair [11, 12]. TNFα, the most potent pro-inflammatory cytokine in the pathogenesis of RA thus stimulates the production of RANKL and DKK-1, and thus promotes resorption and suppresses formation of bone in the joints. Immobilization and reduced mechanical loading due to pain-related morbidity are additional factors contributing to bone loss in RA. Several studies have demonstrated generalized osteoporosis with increased risk of fracture in RA patients compared with control [13-15].

There are three general classes of drugs commonly used in the treatment of RA including corticosteroids, non-steroidal anti-inflammatory agents (NSAIDs) and disease modifying antirheumatic drugs (DMARDs). The onset of action of corticosteroids and NSAIDs is rapid (a couple of weeks) and at best display symptomatic relief while DMARDs can take a few months to manifest a clinical effect but have shown significant improvement in RA pathology and could eventually lead to cure. A deeper understanding of immunologic and pathophysiologic mechanisms of RA gave rise to the introduction of biologic DMARDs into routine clinical practice for patients with severe RA. Because of the dramatic efficacy of biologic DMARDs in mitigating disease states in RA, a considerable effort has been placed in last few years to study whether these agents could be discontinued or dose tapered off. This review will discuss various chemotherapeutic agents that are used in RA with special emphasis on biologic DMARDs and various considerations for their withdrawal as some of these agents have significant risk of triggering serious bacterial infections and high treatment cost.

Pharmacological strategies

Pharmacotherapy for RA makes use of corticosteroids, NSAIDs and disease modifying antirheumatic drugs (DMARDs). The onset of action of corticosteroids and NSAIDs is short compared to DMARDs, which can take several weeks or months to manifest clinical efficacy. A summary of these three drug classes are given below.

Corticosteroids

Synthetic corticosteroids that are generally used for their anti-inflammatory and immunoregulatory activity include prednisone and methylprednisolone (MP). Corticosteroids are used as adjunct therapy in early stages of the disease with NSAIDs or DMARDs. However, corticosteroids are difficult to discontinue once started and need to tapered off. Major adverse effects of prednisone include weight gain, increased blood pressure, insulin resistance, increased risk of cataracts, avascular necrosis of bones and osteoporosis with increased risk of fracture [16]. To avoid systemic effects of corticosteroids, intra-articular injection of the drug could be effective in controlling RA flare in monoarticular synovitis [17].

NSAIDs

This class of drugs reduce acute inflammation to impart an analgesic effect thus improving

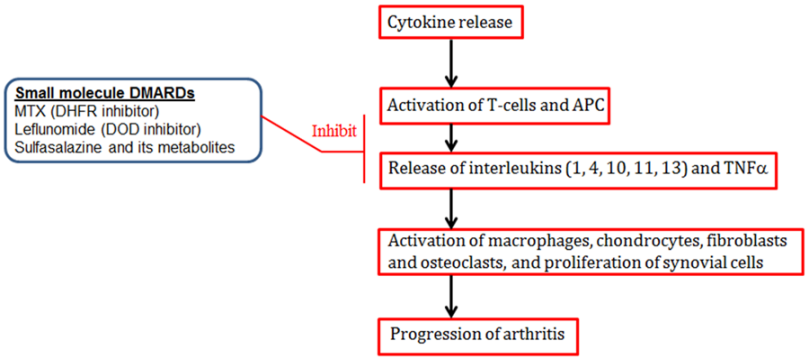

Figure 1. Summary of mechanism of action of widely used small molecule DMARDs. MTX is a folic acid antagonist (acts by inhibiting dihydro-folate reductase, DHFR). Leflunomide inhibits pyrimidine synthesis in T lymphocytes (acts by inhibiting dihydroorotate dehydrogenase, DOD). Sulfasalazine exerts immune-suppressive effect by pooling adenosine. All three drugs inhibit activation of T cell and antigen presenting cells (APC), and consequent augmented release of pro-inflammatory interleukins and TNF. By these mechanisms, these DMARDs suppress activation of target cells in the joint and mitigate progression of RA.

mobility and function. However, these drugs do not prevent joint destruction and thus do not alter the course of RA [18]. NSAIDs inhibit the production of prostaglandins (PGs) by blocking cyclooxygenases 1 and 2 (COX-1 and COX-2). PGs are mediators of inflammation and pain [19]. Because PGs have important physiological including protection from gastric acid, maintenance of kidney perfusion, and contributing to platelet adherence and vascular function, blocking their production has adverse effects in multiple organs such as gastrointestinal bleeding, impaired renal function and hypertension. Selective COX-2 inhibitors have shown safer gastro-intestinal (GI) profiles than conventional non-selective NSAIDs [20, 21]. Largely owing to their serious side effects and lack of disease modifying effect, NSAIDs are not prescribed long-term.

DMARDs

Whereas NSAIDs improve RA symptoms, only DMARD agents have been shown to alter the disease course and improve radiographic features. Among various DMARD agents, methotrexate, sulfasalazine, leflunomide and hydroxychloroquine are commonly used small molecule drugs. Methotrexate is an anti-folate used in cancer chemotherapy but has also shown significant efficacy in RA treatment, however, the mechanism by which the drug improves RA is not understood [22]. Methotrexate may have inhibitory effect on the pro-inflammatory cytokine, interleukin -1 (IL-1), and could alter arachidonic acid metabolism and suppress proteolytic enzymes [23]. Direct inhibitory effect on the proliferation of synovial cells has also been reported [24]. Methotrexate has several serious side effects albeit rare including liver cirrhosis, interstitial pneumonitis, and severe myelo-suppression. The mechanisms of action of hydroxychloroquine and sulfasalazine in altering RA progression are unknown. Leflunomide is a competitive and reversible inhibitor of dihydroorotate dehydrogenase, a mitochondrial enzyme required for the production of intracellular pyrimidines, thereby restricting DNA and RNA synthesis in activated lymphocytes, and prevent them from entering into S phase of cell cycle [25, 26]. Leflunomide also inhibits protein tyrosine kinases in proliferating T and B lymphocytes and subsequently down-regulates immunoglobulin production [27, 28]. **Figure 1** provides a summary of the cellular mechanisms underlying the inhibitory effect of small molecule DMARDs in the progression of RA.

While the small molecular DMARD agents act by mechanisms that are uncertain, advent of biologicals to specifically target functions of major cytokines causing inflammation in RA including TNFα, IL-1 and IL-6 have radically changed the treatment outcomes. In addition, modifying the functions of the participating lymphocytes in RA pathogenesis such as T- and B-lymphocytes also has significant advancement in the treatment of RA [29, 30]. TNF is produced by macrophages and lymphocytes, and is found in large quantities in the joints of RA patients. TNF mediates joint damage and destruction due to activation of matrix metalloproteinases and RANKL production from T-lymphocytes. Presently, five varieties of TNF inhibitors have been approved by the U.S. FDA out of which three are monoclonal antibodies (adalimumab, golimumab and infliximab), one is

Table 1. Salient features of various biologic DMARDs

Drug class	Approval year	Structure	Dose and route of administration
TNF antagonist	Etanercept (1998)	Fc portion of human IgG1 linked to soluble fusion protein of 2 recombinant p75 TNFα receptor	25 mg twice weekly or 50 mg once weekly; s.c.
	Infliximab (1999)	Chimeric Mab with Fc region of human IgG1 joined to variable region of mouse anti-TNFα antibody	3 mg/kg over 2 hours by IV infusion at weeks 0, 2, 6, and then every 8 weeks with dose adjustment up to 10 mg/kg if necessary
	Adalimumab (2002)	Recombinant human IgG1 Mab against TNFα	40 mg every 2 weeks; s.c.
	Certolizumabpegol (2009)	PEGylated humanized monoclonal anti-TNF Fab fragment	400 mg at 0, 2, 4 and then 200 mg every other week; s.c.
	Golimumab (2009)	Human anti-TNF receptor Mab	50 mg once a month; s.c.
IL-1 inhibitor	Anakinra (2001)	Recombinant IL-1 inhibitor that prevents binding of IL-1 to its receptor	100 mg daily; s.c.
IL-6 inhibitor	Tocilizumab	Humanized Mab to IL-6 receptor that prevents binding of IL-6 to membrane-bound and soluble IL-6	4 mg/kg or 8 mg/kg every 4 weeks; IV infusion
B-cell depletion therapy	Rituximab (2006)	Chimeric human/mouse anti-CD-20 Mab	1000 mg IV infusions twice two weeks apart
T-Cell co-stimulation blocker	Abatacept (2005)	Rombinant fusion protein consisting of the extracellular domain of human CTLA-4 and a region of Fc protion of human IgG1	IV infusions of 500-1000 mg at weeks 0, 2, 4 and then every 4 weeks
RANKL inhibitor	Denosumab (2012)	Monoclonal human anti-RANKL antibody	Twice yearly; s.c.

Mab, monoclonal antibody; IV, intravenous; s.c., sub-cutaneous.

Table 3. Summary of representative studies for discontinuation of biologic (infliximab) in RA patients where chemical DMARD was methotrexate

Study	Country	Criteria	Observation time (years)	No. of discontinuations	Failed (%) or resumed	Effect of resuming biologic	References
TNF20	UK	None (randomized)	8	10 (1 died); 4/9 remission; ¼ drug free	5/9; 56	NS	[103]
RRR	Japan	DAS28 ≤ 3.2 at > 24 wk	1	114 discontinued and 102 assessed at 1 year	46/102; 45%	NS	[82]
BeSt	Netherlands	DAS28 ≤ 2.4 at 24 wk	7.2	77/148 (52%)	48% resumed; 17 months (median duration)	84% DAS	[104]
BeSt	Netherlands	DAS28 ≤ 1.6 at ≥ 24 wk	5	115/508 (23%)	53/115 (46%) resumed; 23 months (median duration)	39/53 (74%) DAS < 1.6	[81]
BeSt	Netherlands	DAS28 ≤ 2.4 at ≥ 24 wk	2	66/117 (56%) initially on biologic	NS	NS	[105]
BeSt	Netherlands	DAS28 ≤ 2.4 at ≥ 24 wk	2	19/67 (29%); delayed infliximab 67/120 (56%) median duration 9.9 months	10/67 (15%) resumed; median duration 3.7 months	NS	[106]

BeSt, Behandel (treatment) strategies; DAS, Disease Activity Score, RRR, remission induction by Remicade in R.

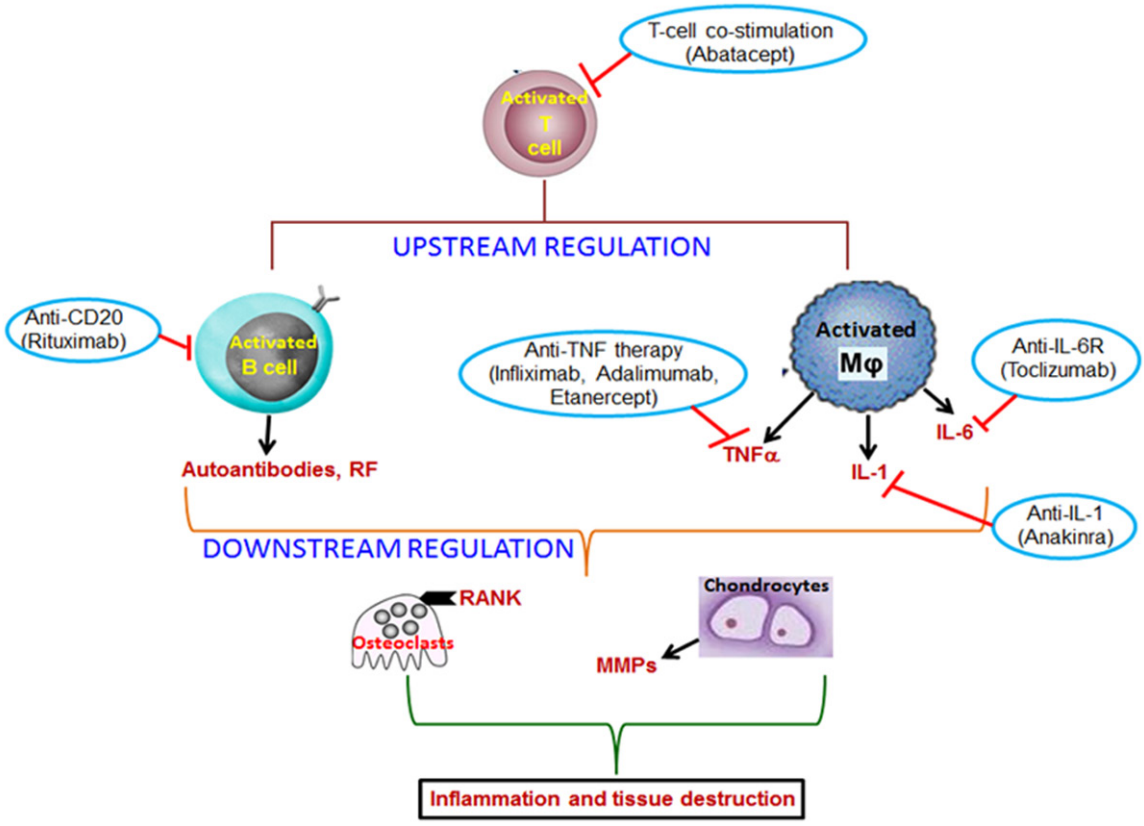

Figure 2. Activated T cells in response to self-antigen activate B lymphocytes and macrophages (Mϕ). Abatacept is a fusion protein that binds to CD80 and CD86 receptors on APC to inhibit T cell activation. Activated T cells act as a crucial upstream regulatory process to induce immunological responses of B cells through increased production of autoantibodies and rheumatoid factors (RF), and abatacept also suppresses downstream B cell activation. Mfϕ activation is also suppressed by abatacept as a result of T cell suppression. Rituximab is a targeted B cell therapy that acts by depleting CD20+ B cells. Various anti-TNF therapies (infliximab, adalimumab and etanercept), anti-IL6R (toclizumab) and anti-IL-1 (anakinra) act by neutralizing pro-inflammatory cytokines release by activated Mf. Downstream regulation represents final common pathway of joint destruction executed by osteoclasts (bone destruction) and chondrocytes (by secretion of matrix metalloproteinases, MMPs). Black arrows - increased secretion and red lines - inhibition/neutralization.

a soluble TNF receptor-Fc immunoglobulin fusion construct (etanercept) and the fifth is an anti-TNF antigen binding domain-polyethylene glycol construct (certolizumab pegol) [31, 32]. Details of clinically used TNF inhibitors including molecular structure, drug dose and route of administration are given in **Table 1**.

Several biologic DMARDs other than TNF inhibitors have been introduced for RA treatment. Abatacept is the first of a class of agents that blocks T-cell co-stimulatory effects by interfering with the interactions between antigen-presenting cells and T lymphocytes thereby modifying early stages in the pathogenic cascade of events in RA. A fusion protein, abatacept is a combination of the extracellular domain of CTLA4 (CD154) with the Fc portion of a human immunoglobulin. CTLA4 has very high affinity for CD28. As a result, abatacept binds to CD28 on the T cell surface and thereby prevents the generation of the second signal required to activate T cells. An additional effect of abatacept is to decrease the production of T cell derived cytokines including TNF [33].

B-cellsby acting as APC, differentiate into antibody-forming plasma cells, interact with T-cells and secrete cytokines, and together contribute to the pathogenesis of RA. Thus, B-cell depletion is a reasonable strategy for RA treatment. Rituximab, a monoclonal antibody against CD20 protein that was originally developed for the treatment of non-Hodgkin's lymphoma has

Table 2. Recommended approach of RA treatment with DMARDs

• One or more DMARDs (preferably, a small molecule and a biologic)
• Principal short term objectives are symptom alleviation and prevention of joint damage
• Long term goals are to achieve remission or at least LDA
• Therapeutic efficacy should be assessed regularly and adjusted if response is low or absent
• No progression of radiologic features of joint destruction should be insured

been repurposed to treat RA as clinical trials data showed reduced signs and symptoms of radiographic progression of RA patients who have failed to respond to other DMARD agents including methotrexate and TNF inhibitors [34]. Rituximab is a chimeric protein consisting of approximately 20% mouse and 80% human protein and depletes mature and pre-B cells but spares stem cells, pro-B cells and plasma cells as they don't express CD20 [35, 36]. In RA patients, rituximab completely depletes peripheral B cells and variably depletes B cells in synovium and other sites [37]. A major adverse effect of rituximab is reactivation of dormant viral infections including hepatitis B [38].

IL-6 is a pleiotropic inflammatory cytokine produced by lymphocytes, monocytes, fibroblasts, synovial and endothelial cells. IL-6 not only induces systemic inflammation but also joint inflammation by T-cell activation, induction of immunoglobulin secretion, increased hepatic acute phase protein synthesis and stimulation of hematopoietic precursor cell proliferation and differentiation. Because of its potent inflammatory effect, IL-6 is a therapeutic target for RA [39]. Antibody raised against IL-6 binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors. Tocilizumab is an example of IL-6 inhibitor which is recommended as monotherapy or with other DMARDs [40]. Tocilizumab, in addition to having increased risk of infection has been reported to cause reduced platelet count, impair liver function, dyslipidemia and neutropenia [32].

IL-1 is a potent inflammatory cytokine that causes cartilage degradation and activates osteoclasts leading to subchondral bone erosion. IL-1 receptor antagonist (IL1Ra) is an endogenous blocker of the cytokine. However, an engineered IL1Ra has an N-terminal methionine in native IL1Ra (anakinra) that competitively blocks the biologic activity of native IL-1 by binding to IL-1 receptor. Clinical trials have shown that anakinra reduces radiologic progression of RA and its combination with methotrexate is well tolerated and better than methotrexate alone [41-44]. In addition to increase in infection risk, anakinra has been shown to cause decrease in neutrophil counts [45]. Mechanism of actions of major biologic DMARDs are shown in **Figure 2**.

Use of DMARDs, either synthetic or biologics has strikingly improved the disease outcomes of established RA. Implementation of early aggressive and dynamic treatments including dose step up and targeted treatment strategies until low disease activity (LDA) or remission is achieved appears to have paid dividends [46-49]. **Table 2** provides recommended approach of RA treatment with DMARDs. Given the achievement of LDA or prolonged remission tapering or discontinuation of drug is now a distinct possibility compared to the perception of recent past that RA treatment should be given lifelong as its discontinuation would result in relapse [50-52]. Also, with improvements in RA prognosis with DMARDs, the risks or adverse effects of DMARD continuation such as the risk of serious infections and costs could outweigh the benefit of treatment continuation [48, 53]. Owing to these reasons tapering of RA therapies has been included in the 2013 guidelines of European League Against Rheumatism (EULAR) for the management of RA [54]. We would now discuss why, how, and in whom tapering/discontinuation of treatment could be considered based on the available evidence.

Response predictors of biologic DMARDs

Available data show that 30-40% RA patients receiving biologic DMARDs do not respond [55, 56]. Because biologic DMARDs are associated with opportunistic infections and other adverse effects [57] and thus exposing non-responders to unnecessary adverse effects of this class of therapy should be avoided. Patients are generally prescribed TNF inhibitors as the first line of biologic DMARD and observed for 3-6 months,

and in case of insufficient improvements in disease activity, they are switched to another biologic and response is monitored for similar length of time as before. This trial-and-error approach is fraught with uncertainty as patients could progress to irreversible joint damage along with suffering from other toxic effects of the drugs and also bear very high expenses of these therapies [57]. Under this situation, there is a need for a more accurate strategy to predict response to specific treatments prior to start of treatment which will guide the optimal choice for each patient. This personalized approach could significantly reduce disease activity and treatment risk, and bring down the healthcare costs due to frequent monitoring, and managing complications and morbidity associated with lack of response to drugs. Response prediction is established in oncologic diseases viz. Her2 receptor expression and response to trastuzumab in breast cancer, wherein Her2 receptor overexpression patients (occurrence if 15-20%) are predicted to respond to the drug [58, 59]. However, presently there is no clinically useful baseline marker that could predict patient response to biologic DMARDs so as to develop personalized treatment.

However, in patients with anti-citrullinated protein antibody (ACPA) positivity, rituximab showed greater response over ACPA negative patients [60-62]. Further, GG genotype in the TNFα gene with G>C polymorphism was found to be associated with infliximab TNF inhibitor therapy [63]. On the other hand, -308 G>A polymorphism of TNFα gene was found to be poorly associated with TNF inhibitory therapy [64]. A meta-analysis studying whether TNFα promoter -308 A/G and -238 A/G polymorphisms and shared epitope status were associated with TNF inhibitor responsiveness in RA patients found that -238 A/G but not -308 A/G polymorphisms was associated with infliximab treatment or shared epitope status [65]. From these data, it appears that the added value of gene TNFα gene polymorphism with respect to treatment response remains premature.

The case for why treatment relaxation can be considered

When baseline disease activity score 28 (DAS28) was considered, methotrexate monotherapy or in combination with TNF inhibitor significantly lowered baseline DAS28, and displayed a more than twofold increase in 6-month remission in RA groups [66]. Therefore, maintaining patients at full dose could be viewed as "over-treatment", and hence treatment reduction in such cases is suggested. In addition, when remission does not represent a cure, dose reduction or "treatment holiday" could be considered. Also, dose reduction would represent a better benefit-to-risk profile as patients would be at a lesser risk for contacting severe infection.

A pharmacodynamics rationale also lies with DMARD reduction. Generally, biologic DMARDs manifest their action after achieving a minimal serum concentration [67]. Therefore, it is conceivable that in each subjects, a dose-response curve (disease activity in response to drug dose/serum concentration) exists with a LDA at a higher drug dose. There could be several possibilities in dose-response curve: a) normal, b) partial, c) curve shifted to the right (higher dose required for effect), d) shifted to the left (effective at lower dose) and e) no response (drug is ineffective or patient improved without the drug). In case of the last group, drug should be tapered off or discontinued as there is no expected consequence of the drug on disease activity. In addition, within a patient, sometimes dose-response could alter due to secondary reasons resulting in spontaneous improvement of disease activity, and in which case treatment relaxation can be considered. However, when a flare occurs after tapering, it may not be attributed to lower dose as it could be the natural evolution of the disease. Finally, there is an economic factor associated with tapering biologic DMARDs as the cost incurred by the patient as well as the country is substantial [68-70].

Strategizing drug tapering

Recent criterion of remission is based on DAS28 with mean LDA or remission duration of usually at least 6 months. The definition of flares varied from relapse in one or more joints with clinical synovitis, loss of LDA remission or LDA associated with DAS28 change of > 0.6 or 1.2, thus suggesting significant heterogeneity in considering flares [71]. Several small molecular (non-biologic) DMARDs including methotrexate, azathioprine, penicillamine and gold

monotherapies were evaluated following withdrawal in RA patients after achieving remission [72-77]. In total 501 patients were enrolled and followed up for 24 months. In one RCT, penicillamine was tapered and in the rest DMARDs were stopped [72]. The impact of withdrawal was evaluated in a meta-analysis, which showed that discontinuation resulted in 46% flares compared to 17% in the treatment continuation group [51]. These meta-analyses suggested that patients in whom DMARDs has been withdrawn are at 2.7-fold more risk of flares compared to those remaining with DMARDs. In a follow up study, the effect of DMARD resumption after incidences of flares post-withdrawal was assessed. A significant decrease in disease activity measures was noted within 3 months of treatment resumption [78]. By 12 months 35% of patients had complete remission and 43% showed mild disease activity. However, 8% of patients were unable to benefit from resumption of treatment. However, these studies suffered from the following caveats: small, included old generation DMARDs (rare used now) and defined flares in a variety of ways [78].

Three RCTs assessed tapering combination of DMARDs given as sequential monotherapy wherein the strategies were to step down following intensive therapy in early RA. In the first study (COBRA trial), high dose prednisolone was given for 28 weeks followed by low-dose methotrexate for 40 weeks and thereafter patients were maintained in sulfasalazine therapy [79]. Controls received sulfasalazine monotherapy. Both disease activity and erosive progression showed better outcomes with combination DMARDs. Further, patients who received a 6-months cycle of intensive initial treatment were better controlled on radiological progression after tapering over the next 4-5 years compared with controls [79].

In The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial, efficacy and tolerability of combination of sulfasalazine, methotrexate, hydroxychloroquine, and low-dose prednisolone was compared with the same DMARDs as monotherapy with or without prednisolone in patients with early and active RA. Induction of remission, achievement of clinical improvement (as per American College of Rheumatology [ACR] criteria of 50% clinical response) and joint radiological outcomes were efficacy measures. Data showed that most patients with intensive treatment achieved remission and 11-year follow up study showing lesser radiologic damage in patients treated with initial combination of DMARDs compared to monotherapy group [80].

In another study that used 5-year data from the BeSt study, in which 508 patients with recent-onset RA were randomized into four treatment arms comprising of DMARD monotherapy, step-up combination, step-down combination (derived from COBRA regimen) and methotrexate in combination with infliximab [81]. Efficacy measure was DAS $\leq$ 2.4 and when DAS was < 1.6 for six months or more, DMARD was tapered or discontinued. In cases where DAS was increased to 1.6, the last DMARD was immediately resumed. Results concluded that nearly 25% patients had drug-free remissions whereas 46% resumed treatment for increased DAS and in whom a majority achieved radiologic remission within 3-6 months of resumption of treatment [81].

In a multicentre study, the effect of infliximab withdrawal in patients with RA after they achieved DAS-recommended LDA, including those with long-standing disease was assessed (remission induction by Remicade in RA, RRR). The data suggest that after achieving LDA, discontinuation of infliximab for > 1 year had no progressive radiological articular destruction in 56 (55%) of the 102 patients [82]. **Table 3** provides summary of representative studies from U.K., Japan and the Netherlands on discontinuation of infliximab in RA patients where chemical DMARD was methotrexate.

In HONOR study, RA patients who achieved DAS28-erythrocyte sedimentation rate (ESR) remission for 6 months with adalimumab (a monoclonal antibody against TNF) in combination with methotrexate were studied for 1 year [83]. The data showed that adalimumab could be discontinued without flaring in 79% patients with deep remission (DAS28-ESR $\leq$ 1.98), which was similar to the group receiving the drug. Also, for patients with flare, drug re-administration was very effective. Tocilizumab is a humanized monoclonal antibody against IL-6 receptor. In study consisting of RA patients having median disease duration of 7.8 years and prior tocilizumab treatment period of 4.0

years with DAS28 of 1.5, LDA could be maintained for 1 year after treatment discontinuation in 70% RA patients. Moreover, the study also showed that serum IL-6 and MMP-3 levels are good predictors of flaring after discontinuation [84]. From these data, it appears that "drug holiday" in the category of biological DMARDs in RA patients with significant improvements in DAS28 could be contemplated.

The evolution of RA treatment over the past decade has given traditional step-up regimens to more aggressive approaches. Central to the change in approach include hit early (early start of treatment), hit hard (steroids with rapidly escalated biologics) and frequent measurement of disease activity and act accordingly. These treatment approaches have significantly increased achievement of LDA in most patients with attenuated joint damage and improved quality of life. For example, infliximab was decreased by 25% of the original dose (3 mg/kg) every 8-12 weeks with no change in the interval of dosing until discontinuation or appearance of flare in RA patients who received stable treatment for > 6 months and had low DAS28 score. The study monitored these patients for 1 year and the results showed that dose reduction was feasible in 45% patients with a mean dose reduction of 60%, and complete discontinuation was possible in > 15% patients [85]. This study also revealed that RA patients with long disease duration due to late treatment intervention are at a risk of greater relapse than those received early intervention. However, in PRESERVE study funded by Pfizer has shown the benefit of continuation of etanercept either in full-dose or half-dose compared with its discontinuation in established RA patients who achieved low DAS28 score with etanercept and methotrexate combination [48]. These results were essentially confirmed by the CERTAIN (certolizumab pegol) study wherein patients with established RA (MTX-IR) flared with withdrawal of the biological [86]. In a study comprising of 180 RA patients with treat-to-target protocol (objective was to maintain at least LDA) a disease activity-guided reduction of adalimumab or etanercept dose observed successful outcome with regard to major flaring, and ultimately led to successful dose reduction or discontinuation in two thirds of patients [87].

In the recently published 78 week randomized double blind Optimal Protocol for Methotrexate and Adalimumab Combination Therapy in early Rheumatoid Arthritis (OPTIMA) trial that was carried out at 161 sites worldwide the efficacy and safety of adalimumab plus methotrexate was compared with methotrexate monotherapy and followed up for 26 weeks [88]. Here methotrexate naïve patients with early stage RA having disease duration < 1 year were given wither methotrexate alone or methotrexate and adalimumab combination (induction therapy) for a period of 26 weeks (group 1). After 26 weeks, patients who achieved stable LDA (DAS28 < 3.2) were randomized either to maintain or to stop adalimumab, and were followed for another 52 weeks (group 2). Significant improvements in clinical and functional outcomes were observed as early as second week and continued to 26th week with induction therapy. 20% patients in this therapy group achieved stringent remission according to the new ACR/EULAR definition within 6 months of treatment initiation, and an additional 30% achieved LDA.

The study also showed that methotrexate monotherapy achieved significant LDA. Early intervention with induction therapy was also effective in giving substantial protection from radiographic damage compared with methotrexate monotherapy. These results reiterate the use of methotrexate in combination with TNF inhibitors as a treatment option with substantial therapeutic benefits in patients with early, active RA. Clearly, the benefit was often maintained after adalimumab discontinuation: 82 of 101 patients had DAS28 < 3.2 at week 78, suggesting that methotrexate alone effectively maintains low LDA in most patients following successful induction therapy. The High Induction Therapy with Anti-Rheumatic Drugs (HIT HARD) study is a similar but smaller study than OPTIMA, but results were similar, i.e. methotrexate continuation is effective in a significant patient population for sustained remission after the cessation of biologic DMARDs [89].

Progressive spacing of biologic DMARDs is a practical strategy as difficulty related to lack of half-dose packaging does not come in the way. In a single centre open label study, drug spacing was done in patients who had remission (DAS28, ESR < 2.6) for at least 3 months under tocilizumab therapy. Initially a 6 weeks spacing in the first 3 months was given and if no flare was observed then 8 weeks spacing for 2 more infusions was given. 35% patients displayed

prolonged remission and 64% had relapse after spacing. Among the relapse group, > 40% had erosion. Authors of the study concluded that tocilizumab spacing appeared feasible for patients with prolonged remission and this approach may not be applied to patients with high disease severity, particularly erosion [71]. Data on the maintenance of Drug-free Remission among patients treated with tocilizumab Monotherapy (DREAM study) show that 10% of patients were able to discontinue tocilizumab therapy. Low matrix metalloproteinase 3 and low serum IL-6 levels were predictors of LDA [84]. In STRASS (Spacing of TNF-blocker injections in Rheumatoid Arthritis Study), the effect of progressive spacing of TNF blockers (etanercept or adalimumab) was compared with treatment continuation for established patients with RA showing remission [90]. The study duration was 18 months and the patients received stable dose of TNF blockers for ≥ 1 year, and displayed remission in DAS28 score for ≥ 6 months. Patients were randomised into two groups: treatment continuation or treatment spacing by 50% every 3 months up to complete discontinuation. In case of relapse, the treatment dose and regimen was restored to the initial level. An important finding of this trial is the feasibility of implementing step-down approach in 75% (48 out of 76) of the patients with 39% patients showing no relapse even after complete discontinuation. Major limitation of the study was the failure to identify any predictor of relapse or dose tapering [90]. In a Disease Activity Guided Dose Reduction study (DRESS) the effect of stepwise increase in the treatment interval of adalimumab or etanercept until relapse of disease activity or discontinuation was compared with treatment continuation (no dose reduction). Primary outcome measure was major flare longer than 3 months [DAS28-C-reactive protein (CRP)] between the two groups at 18 months. The study concluded that dose reduction approach of TNF blockers to treat RA is non-inferior to treatment continuation in terms of major flaring, and successful dose reduction or complete discontinuation was possible in 66% of patients [87]. A DRESS protocol study in two Dutch rheumatology outpatient clinics performed cost-effectiveness analysis with TNF blockers and concluded significant cost saving with no loss of quality of life in RA patients [91].

In a randomized control study (RETRO trial) [92], both small molecule and biologic DMARD-treated patients with established RA were included after they achieved DAS28 remission for > 6 months and followed up for 1 year. Randomization groups were: 1) all DMARDs continued at full dose; 2) half reduction in dose of all DMARDs either by increased drug spacing or decrease in dose keeping the same frequency of administration; and 3) stopping all DMARDs in patients with half reduction in dose after 6 months. Data showed that the risk of relapse was 16% in group 1, 39% in group 2 and 52% in group 3, which suggested that more aggressive the dose reduction strategy, the greater the risk of relapse. Patients with anticitrulinated antibodies were at a greater risk of relapse. At the end of the follow up 6%, 16% and 15% patients were in remission or LDA in groups 1, 2 and 3, respectively and the observed differences in number between the groups were not significant. The study did not include structural damage data. Although the study population was heterogeneously treated with different DMARDs and the change of all DMARDs done at the same time which added complexity to outcome interpretation, yet the RETRO trial confirmed the feasibility of DMARD tapering for a significant percentage of patients [92].

Which patients are eligibility for drug tapering and its timing?

The 2013 EULAR clinical practice guidelines for the management of RA patients has recommended considering DMARD reduction upon achievement of therapeutic target [93, 94]. Most notably, the guideline states that in patients where prolonged remission is observed after reduction in glucocorticoid dose then tapering biologic DMARD could be considered especially if this treatment is combined with any small molecule DMARD. In case of even longer remission, cautious reduction of the small molecule DMARD could also be considered by the physicians, if agreed by the patient. However, there is a recommendation for specific sequence for treatment reduction: 1) decreasing glucocorticoids due to serious risk of infection, long-term and cumulative risk of cardiovascular comorbidities, and development of severe osteoporosis when glucocorticoid dose is > 7.5-10 mg/d; 2) reduction in bio-

Table 4. Points to be considered for treatment discontinuation/tapering in patients on biologic DMARDs

• Study designs consideration: complete withdrawal or dose tapering or extension of the interval between administrations of biologic DMARDs
• Any predictors of response following therapy discontinuation or tapering identified
• Goal of treatment before withdrawal: remission or LDA or other and the definitions used for the goals
• Duration required for the patients to achieve goal before a given biologic DMARD was discontinued
• Duration of RA among the enrolled patients
• Type of prior treatments given to enrolled patients
• Disease activity level prior to biologic DMARD therapy initiation and the extent of improvement achieved by the therapy before discontinuation
• Mode of discontinuation of drugs including corticosteroids, NSAIDs and chemical DMARDs which usually accompany biologic DMARDs
• Criteria of defining success vs. failure of treatment; DAS, simple disease activity index (SDAI), clinical DAI (CDAI), radiological tissue damage assessment or functional status assessed by health assessment questionnaire
• Follow up duration
• Effect of treatment resumption; response achieved and the time required for it
• Incidence of serious flaring such as joint damage and mobility impairment among patients who discontinued or reduced therapy

logic DMARD despite they were key contributor to achieving remission; and 3) reduction of small molecule DMARDs.

The major criterion for DMARD reduction is sustained remission over at least 6 months. As no specific criteria are available for decision on DMARD reduction due to lack of consensus on the tool and threshold to assess, therefore, such decision should be taken by an expert rheumatologist rather than relying on high-level literature evidence [93, 95]. All studies on discontinuation and tapering used DAS28 definition of remission or LDA to recruit patients where absence of synovitis was considered as the clinical feature although some studies included synovitis. This criterion could be explained in part due to design feasibility and in part because the study designs were made before the recent remission definition by the American College of Rheumatology (ACR)/EULAR according to the Boolean definition or the Simplified Disease-Activity Index (SDAI) [96]. The remission definition was designed to accurately identify patients with favourable outcomes - no functional limitation based on health assessment questionnaire and no radiological structural damage progression. However, achieving such a remission definition in established RA is not very common except only in a small subset of patients [97]. Therefore, presently no study is available which used ACR/EULAR definition of remission for DMARD discontinuation or tapering. In this regard, it should be noted that in the RETRO trial where ACR/EULAR Boolean remission criteria was largely satisfied, the association with a lower risk of relapse after DMARD tapering in patients with DAS28 < 2.6 for at least 6 months may be premature [92]. Similarly, in the DRESS study, baseline disease activity which ranged from DAS28 CRP 0.96-3.8 was not a predictor for successful DMARD dose reduction [98]. In addition, a score of ≤ 1 on the patient global assessment (PGA) with a 0-10 scale as RA remission as required in the Boolean definition was found challenging and thus some clinical investigators proposed a new definition to identify patients with similar good outcomes ("near remission" state) and who report to clinic in a relatively greater number than the Boolean definition criteria [99]. Therefore, it is reasonable to attempt tapering to those RA patients who are in remission or at least achieved LDA and continuing without relapse instead of increasing the dose or switching to other DMARD. **Table 4** enumerates salient points to be considered for withdrawal or dose reduction of biologic DMARDs.

Absence of clinical signs of inflammation to remain as criteria for remission is being questioned these days as low levels of continuing joint destruction could occur. It is proposed that inclusion of available advanced imaging techniques could successfully aid in defining remission more accurately. Several reports suggest that persistent subclinical inflammation could be to a certain extent predictive of poor outcome in RA patients in remission. In this regard, increased risk of relapse with positive Doppler signal on Power Doppler ultrasound [100] and increased risk of structural damage progression when bone marrow edema is observed on magnetic resonance imaging [101, 102]. Whether imaging assessments of sub-clinical inflammatory activity should be included in the remission criteria to improve

long-term outcomes for patients with RA need further research.

Conclusions

Dose reduction or discontinuation of biologic therapy in patients with RA who have achieved disease remission is an appealing concept from multiple perspectives, including safety and economical issue. A number of clinical trials have been addressing this issue. Evidence from RCTs indicates that sustained remission by biologic DMARDs targeting TNF in MTX-naive RA patients and RA patients with inadequate response to MTX is possible, which raises the possibility of discontinuing treatment and keeping the patients under close monitoring for relapse/flare of RA defined by maintaining LDA without radiologic and progression of articular destruction. At this stage, it is safe to conclude that "drug holiday" of TNF inhibitors is generally possible in patients who received treatment at their early stages of RA, although some fraction of patient population with longstanding RA have also shown remission and thus qualify for treatment discontinuation. However, following analyses of clinical trial data, attempt to arrive at a clinical decision about a unified approach is complicated by heterogeneity among the studies. Nevertheless, some useful information can be obtained from these studies that can serve as the basis for future studies. With more knowledge gathered from additional large controlled trials, it is hoped that clinicians may be in a position to discontinue or taper biologic DMARDs in suitable RA patients while maintaining optimal outcomes.

Despite the possibility of DMARD discontinuation, it should be noted that the risk of flaring is sometimes increased and for which the recommended predictors are IgM-RF and ACPA-positivity. Further research is required to identify additional predictors of sustained LDA with the discontinuation of DMARD so that combining these with the available predictors would allow identification of patients who are most likely to benefit from treatment discontinuation. Present evidence base is evolving and unfortunately provides an incomplete outcome of cessation or continuing DMARD in good responders.

Although with the advent of biologic DMARDs, particularly TNF inhibitors has improved disease outcomes in established RA patients, but only about one-third meet the criteria for clinical remission which calls for novel clinically effective treatments. Because TNF inhibitors pose a significant safety risk in terms of opportunistic infection in patients several alternative therapies, including tocilizumab (a humanized anti-IL-6-receptor monoclonal antibody), abatacept (a blocker of T-cell costimulatory factor), rituximab (a B-cell depleting agent) and denusumab (a fully human RANKL antibody) should be studied to assess whether a drug free state could be achieved in RA patients after insuring LDA.

Disclosure of conflict of interest

None.

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