Strategies for Achieving Drug-Free Remission in Rheumatoid Arthritis

Subjects: Rheumatology

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Rheumatoid arthritis (RA) is a chronic immune-mediated systemic disease, which affects approximately 1% of the population and is characterized by a symmetrical inflammatory polyarthropathy. It has been demonstrated that drug-free remission (DFR) is possible in a proportion of RA patients achieving clinically defined remission (both on cs and b-DMARDS). Immunological, imaging and clinical associations with/predictors of DFR have all been identified, including the presence of autoantibodies, absence of Power Doppler (PD) signal on ultrasound (US), lower disease activity according to composite scores of disease activity and lower patient-reported outcome scores (PROs) at treatment cessation.

rheumatoid arthritis remission drug-free remission b-DMARDs cs-DMARDs tapering

1. Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated systemic disease, which affects approximately 1% of the population and is characterized by a symmetrical inflammatory polyarthropathy [1].

Over recent years, there has been a paradigm shift in the treatment approach in RA from cautious escalation of therapies for symptomatic relief to the early and rapid control of inflammation soon after diagnosis, aimed to prevent structural damage and preserve function. This is in accordance with the ‘window of opportunity’ hypothesis, which suggests that in early RA, aggressive treatment can reverse underlying autoimmunity and induce immune tolerance (thus potentially modifying the disease course) [2]. In clinical practice, this is achieved using a treat-to-target (T2T) strategy. This strategy involves strict monitoring of disease activity using composite measures, e.g., disease activity score (DAS28) resulting in successive escalation of immunosuppressive agents (conventional synthetic and biologic disease-modifying drugs (cs-DMARDs and b-DMARDs, respectively). These drugs are used alone or in combination and with or without corticosteroids to control inflammation [3].

Experience with b-DMARD tapering is largely with tumor necrosis factor inhibitors (TNFis). Tapering of cs-DMARDs, notably methotrexate (MTX), is also desirable for patients concerned about long-term side-effects and the burden of taking tablets/self-injecting if they are well [4][5]. These frequently lead to poor treatment compliance, with approximately 15% of patients self-discontinuing treatment, which itself can lead to increased disease morbidity [5][6].

2. Defining Remission in RA

To be able to identify individuals who are more likely to achieve DFR, we first need to be able to define remission accurately. Remission in RA is currently defined clinically using a cut-off of the DAS28 (disease activity score). It incorporates a mathematical formula comprising the number of tender and swollen joints out of 28 (TJC28, SJC28), a serum marker of inflammation (e.g., C-reactive protein, CRP) and an optional measure of patients' assessment of global health status (PGA) [7].

DAS28-remission has been defined as a score of <2.6 [8][9]. It is the standard measure used in clinical practice; however, it is not a precise assessment of remission. This score and tender joint count assessment may be influenced by physical comorbidities, e.g., osteoarthritis or psychosocial factors. Swollen joint counts may also be inaccurate in remission [10], while objective serological inflammatory markers (ESR and CRP) are non-specific to RA. Furthermore, the DAS28 joint count excludes the feet and ankles, therefore missing active disease in these areas [6]. It has been shown that some patients in remission do still have evidence of subclinical synovitis on musculoskeletal ultrasound (US) [11][12][13][14].

There have been multiple attempts to define clinical remission more stringently, including the ACR/EULAR 2011 Boolean remission criteria (TJC28, SCJ28, CRP and PGA all ≤1) [15][16], CDAI (TJC + SJC + PGA + Physician GA: remission = 0.0–2.8) [17] and SDAI (TJC + SJC + PGA + Physician GA + CRP: remission is ≤5) [18] scores (comprehensive and simplified disease activity scores, respectively); however, these still include subjective measures and potentially inaccurate joint counts [15][18]. The concept of 'deep' clinical remission has been considered (DAS28 < 1.98), which is suggested to reflect the absence of biological inflammation; however, longitudinal outcome data relating to this target have not yet been studied prospectively [19].

Physical examination is known to have a low sensitivity for the detection of mild synovitis, such as that found in clinical remission; however, musculoskeletal US has proven to be an excellent tool to identify subclinical inflammation that is associated with risk of relapse and structural damage [20][21][22]. Despite this, the definition of what constitutes imaging remission remains challenging [13][22][23]. More recently, immunological status has been shown to predict the likelihood of sustained remission in RA [24][25]. This adds another potential dimension to consider when defining the remission state in RA.

Schett et al. [26] have recently introduced the concept of 'multi-level' remission aimed to characterize remission more precisely (**Figure 1**). It involves the achievement of different levels/depths of remission. It suggests that a state of deep remission may be attained if all three categories are achieved; however, this has not yet been used prospectively.

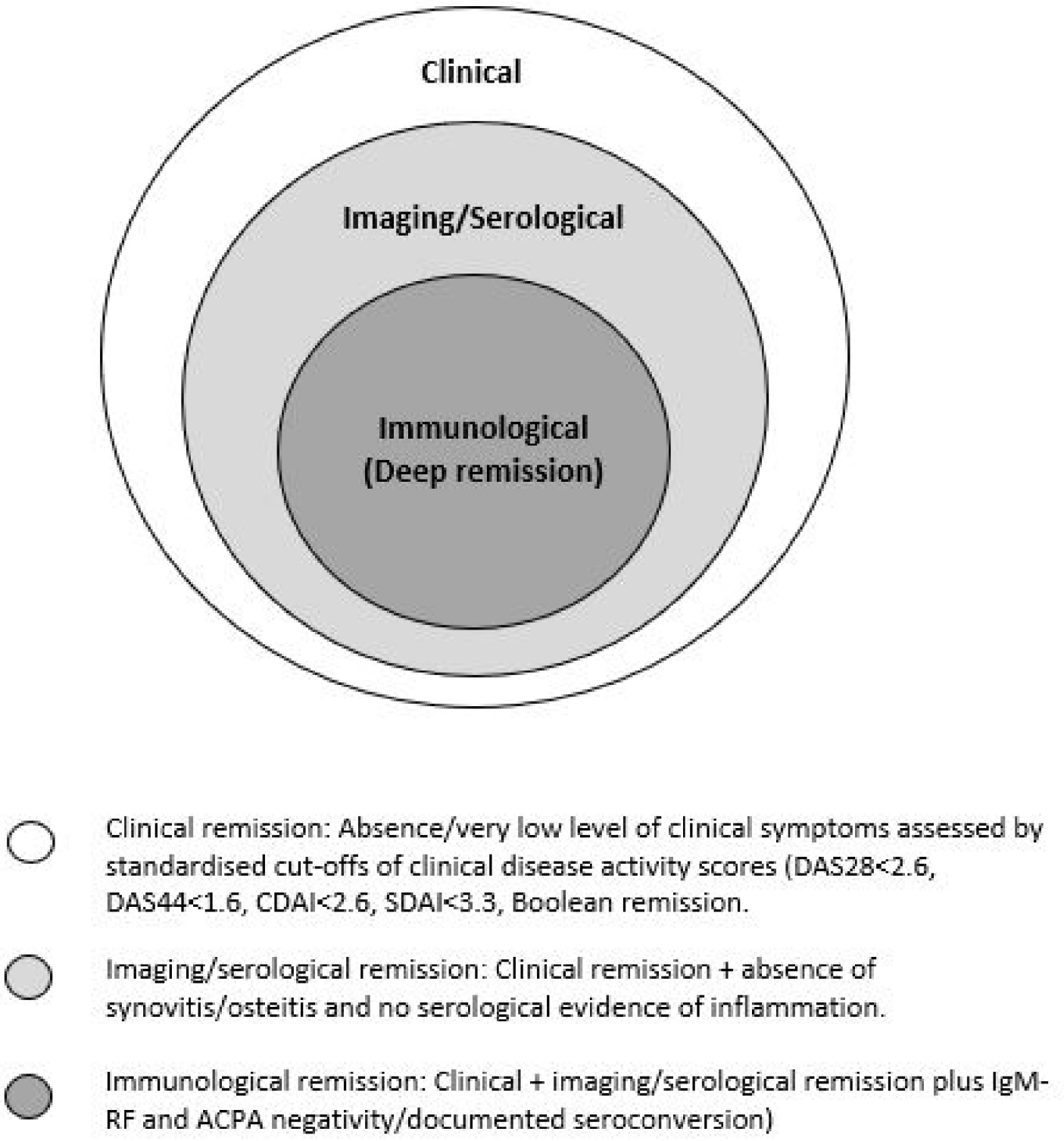

Figure 1. Shell model of remission states [26].

3. DFR Remission in Patients with RA Treated with cs-DMARDs

DMARDs are indicated for the treatment of inflammatory arthritis, e.g., RA; however, they are also used to treat other disorders [27]. cs-DMARDs are typically used as first-line agents, alone or in combination. Commonly used cs-DMARDs include methotrexate (MTX), hydroxychloroquine (HCQ), leflunomide (LEF) and sulfasalazine (SSZ). They are mostly oral preparations (except for MTX, which can also be injected subcutaneously) [28].

Some of the earliest data on withdrawing cs-DMARDS come from historical observational studies. These studies often focus on older conventional cs-DMARDs, which are no longer used in first-line RA treatment, e.g., gold and d-penicillamine [29][30]. It has been demonstrated that DFR is possible in a minority of cases. Most of the evidence for discontinuing cs-DMARDs to achieve sustained DFR comes from randomized controlled trials (RCTs) for patients with stable RA on a range of monotherapies [29][31][32][33][34]. Many of the DMARDs studied, however, are now rarely used in practice. Additional evidence comes from RCTs and observational studies in which a step-down approach in treatment was followed (combination DMARDs reduced to monotherapy). These demonstrated sustained clinical response to treatment after tapering in early RA patients [35][36][37][38].

Table 1 summarizes the studies discussed.

Table 1. cs-DMARD DFR remission studies.

Study	Design	Authors	*n*	Treatment/Intervention	RA Disease Duration	Remission Criteria	%DFR Remission	DFR-Predicting Factors	Follow Up Period
Can disease-modifying anti-rheumatic drugs be discontinued in long standing rheumatoid arthritis? A 15-year follow-up	Observational	Tiippana et al., 2010	70	Single or combination Cs-DMARDS tapered	Early RA	5/6 ARA criteria fulfilled.	16%	N/A	15 years
Prevalence and predictive factors for sustained	Observational	van der Woude et al., 2009	Leiden EAC cohort: 454	Single or combination Cs-DMARDS tapered (MTX/SSZ/HcQ)	Early RA	Had to fulfil 3 criteria: (1) No current use of DMARDs/corticosteroids, (2) No swollen joints,	Leiden EAC cohort: 15%	Absence of autoantibodies ((ACPA and IgM-RF) and short	Minimum of 1 year after discontinuation of DMARD therapy

Study	Design	Authors	*n*	Treatment/Intervention	RA Disease Duration	Remission Criteria	%DFR Remission	DFR-Predicting Factors	Follow Up Period
disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts			British EAC Cohort: 895			and (3) Classification as DMARD-free remission by the patient's rheumatologist.	British EAC Cohort: 9.4%	symptom duration at presentation	
KIMERA	Observational	Jung et al., 2020	234	Single or combination therapy with cs DMARDs; methotrexate (MTX)/sulfasalazine combined with high-dose glucocorticoid; MTX combined with TNF-inhibitors tapered	Early RA	(1) Non-use of cs or bDMARDs and glucocorticoids, (2) DAS28 <2.6, and (3) no swollen joints.	46.1%	Early RA and lower disease activity (DAS28 <2.26) at csDMARD withdrawal	48 months
Randomized placebo-controlled study of stopping second-line drugs in RA	RCT	Ten Wolde et al., 1996	285	Placebo or withdrawal of at least one 2nd line cs-DMARD (chloroquine, HCQ, gold, d-penicillamine, SSZ, AZA or MTX)	Established RA. Median duration 8–9 years.	5/6 ARA criteria fulfilled	62%	Lower maintenance dose of second line drug and absence of RF	52 weeks
D-penicillamine withdrawal in	Double blind RCT	Ahern et al., 1984	38	Tapering of d-penicillamine	Established RA (6–11 years)	5/6 ARA criteria fulfilled	21%	None	12 months

Study	Design	Authors	*n*	Treatment/Intervention	RA Disease Duration	Remission Criteria	%DFR Remission	DFR-Predicting Factors	Follow Up Period
rheumatoid arthritis									
BeST	Multi center randomized single blind trial	Markusse et al., 2015	508	MTX/combination cs DMARD/ combination cs-DMARD +prednisolone/combination cs DMARD with MTX and Infliximab	Early disease (symptom duration < 2 years)	DAS44 <1.6	14%	Absence of ACPA and using MTX rather than SSZ as the last csDMARD before withdrawal	10 years
tREACH	RCT	Kuijper et al., 2016	281	Triple cs-DMARD (MTX, SSZ and HCQ) with glucocorticoid bridging or MTX monotherapy with glucocorticoid bridging TNFi and MTX if the DAS28 was >2.4.	Early RA	DAS28 <1.6	2.4%	N/A	2 year
IMPROVED	RCT	Heimans et al., 2016	610	MTX and prednisolone, then tapered	Early RA or Undifferentiated arthritis	DAS44 <1.6	21%	Absence of ACPA	2 year
BioRRA	Interventional cohort study	Baker et al., 2019	44	Cessation of cs-DMARDs	Established RA	DAS28-CRP < 2.4	48%	Absence of RF, shorter time from diagnosis to starting first DMARD, shorter symptom duration at time of diagnosis, longer disease duration fulfilment of ACR/EULAR Boolean remission	6 months

Mielants, H.; Clerck, L.; Peretz, A.; et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: Validation of the DAS28 score in patients under infliximab treatment. Arthritis Res. Ther. 2005, 7, R1063–R1071.

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Study	Design	Authors	*n*	Treatment/Intervention	RA Disease Duration	Remission Criteria	%DFR Remission	DFR-Predicting Factors	Follow Up Period
								criteria and longer time since last DMARD change Absence of genes within peripheral CD4+ T cells; *FAM102B* and *ENSG00000227070* Presence of gene within peripheral CD4+ T cells: *ENSG00000228010*	

4. Predicting DFR for Patients Receiving Treatment with cs-DMARDs

Several factors have been demonstrated to predict the successful maintenance of remission after cs-DMARD withdrawal to achieve DFR; cs-DMARD-free remission is more likely to be achieved when T2T strategies have been employed with the goal of establishing remission earlier in the RA disease course. This supports the window of opportunity hypothesis for RA treatment [2]. In addition, other factors associated with cs-DMARD-free remission include a longer duration of sustained remission prior to drug withdrawal [13], the absence of autoantibodies (ACPA and RF) [31][39][40] and lower disease activity (DAS28 < 2.6) at the time of treatment cessation [39][40][41][42]. Using methotrexate as the last cs-DMARD before withdrawal has also been associated with a higher chance of achieving DFR [40][43].

The BioRRA study [41] is the most comprehensive study of biomarkers for predicting cs-DMARD remission to date. Baker et al. developed a composite score for the prediction of DFR including circulating inflammatory biomarkers, and peripheral CD4+ T-cell gene expression. This score was able to differentiate future flare from DFR with an AUROC (receiver–operator characteristic) of 0.96 (95% CI 0.91–1.00), sensitivity 0.91 (0.78–1.00) and specificity 0.95 (0.84–1.00). Limitations of the study include small patient numbers and the heterogeneity of cs-DMARDs included. Ultrasound biomarkers were not identified.

Overall, it has been shown that cs-DMARD-free remission can occur in 14–48% of patients achieving remission, although discontinuing cs-DMARDS carries a 38–80% risk of disease flare. This is probably unacceptably high for

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both progression and clinical flare due to the negative impact of flare on QoL [44] and the risk of disease progression [45]; however, it has been reassuringly demonstrated that most patients can re-capture remission following treatment for flare. Identifying patients who can achieve successful withdrawal of cs-DMARDs remains an area of unmet clinical need, despite reports of potential predictive factors in the literature. However, progress in this field is promising.

5. DFR Remission in Patients with RA Treated with Biological Therapies (b-DMARDs)

b-DMARDs can target and inhibit specific pathways of the immune system and inflammatory cascade, each with a unique mechanism of action. TNFis include: etanercept (ETN), adalimumab (ADA), infliximab (IFX), golimumab (GOL) and certolizumab-pegol (CZP). Other agents include rituximab (RTX, anti-CD19 agent), abatacept (ABA, humanized fusion antibody), tocilizumab (TCZ, anti-IL6) and small molecule Janus Kinase (JAK) inhibitors, e.g., baricitinib/tofacitinib, amongst others [27].

Several studies have analyzed the effects of b-DMARD (mainly TNFi) withdrawal in RA patients after a successful remission induction regime and will be discussed. The remission induction regime varies between studies involving different drugs. Furthermore, there is inconsistency in the definitions of remission used; duration of remission; and the duration RA: from DMARD naïve to established RA. Often, drug tapering or successful dose reduction may be the primary outcome. To date, there is no evidence in the literature for discontinuation of RTX or JAK inhibitors.

Table 2 summarizes the studies discussed.

Table 2. Biologic DFR remission studies.

Study	Design	Authors	*n*	Treatment/Intervention *Drug Withdrawn in Italics*	RA Disease Duration	Remission Criteria	%DFR Remission in Biologic Treatment Arm	DFR Predicting Factors	Follow Up Period
IVEA	Double blind RCT	Quinn MQ et al., 2006	20	1. *Infliximab* + MTX 2. MTX	6 months	DAS28	70	-	12 months
BeSt	RCT	van den Broek M et al., 2011	128	4th study arm: Combination with *infliximab*	23 months	DAS44	56	Lower baseline HAQ ACPA negative	24 months

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Study	Design	Authors	*n*	Treatment/Intervention *Drug Withdrawn in Italics*	RA Disease Duration	Remission Criteria	%DFR Remission in Biologic Treatment Arm	DFR Predicting Factors	Follow Up Period
								Lower baseline disease activity Younger age Non-smoker	
IDEA	Double blind RCT	Nam JL et al., 2014	112	1. *Infliximab* +MTX 2. MTX + single dose IV methylprednisolone	78 weeks	DAS44	76%	-	78 weeks
HONOR	Open label non randomized	Yamaguchi A et al., 2020	52	*Adalimumab*	7 years	DAS28	21	A baseline DAS28 of <2.22 or <1.98 Shorter disease duration	60 months
RRR *	Observational	Tanaka Y et al., 2010	114	*Infliximab*	6 years	LDA	55	A baseline DAS28 of <2.22 or <1.98	12 months
OPTIMA	RCT	Smolen J et al., 2013	1032	*Adalimumab* + *MTX*	≤12 months	DAS28	66%	Good baseline functional status	52 weeks

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Study	Design	Authors	*n*	Treatment/Intervention *Drug Withdrawn in Italics*	RA Disease Duration	Remission Criteria	%DFR Remission in Biologic Treatment Arm	DFR Predicting Factors	Follow Up Period
PRIZE	Double blind RCT	Emery P et al., 2014	306	1. *½ dose Etanercept* + MTX 2. Placebo + MTX 3. Placebo alone	≤12 months	DAS2	23–40%	-	39 weeks
CERTAIN	Double blind RCT	Smolen J et al., 2015	194	1. *Certolizumab* + MTX 2. Placebo	6 months–10 years	CDAI	18.8%	-	52 weeks
Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped?	Observational	Saleem et al., 2011	47	*TNFi (Various)* + MTX 1. Initial therapy 2. Delayed therapy	12 months	DAS28	59%15%	Male gender First line TNFi Shorter disease duration Higher and naïve T-cells and fewer IRCs at baseline	24 months
EMPIRE	Double blind RCT	Nam et al., 2013	110	1. *Etanercept* + MTX 2. MTX + placebo	≤3 months	DAS28	28.1%	Starting TNFi earlier in disease course	52 weeks

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Study	Design	Authors	*n*	Treatment/Intervention *Drug Withdrawn in Italics*	RA Disease Duration	Remission Criteria	%DFR Remission in Biologic Treatment Arm	DFR Predicting Factors	Follow Up Period
TARA	Single blind RCT	Van Mulligen et al., 2020	189 94 DMARD 95 TNFi	*TNFi or csDMARD (Various)* *1. csDMARD taper first* *2. TNFi taper first*	Not stated	DAS44	15%	-	24 months
AVERT	Double blind RCT	Emery P et al., 2015	351	*Abatacept + MTX*	<1 year	DAS28	15%	Lower baseline PRO scores	18 months
DREAM	Observational	Nishimoto N et al., 2014	187	*Tocilizumab*	7.8 years	LDA	9%	Lower multi-biomarker assay scores (serological) RF negative	12 months
ACT RAY	RCT	Huizinga TW et al., 2015	556	*Tocilizumab*	8 years	DAS28	6%	Shorter disease duration, few/absent erosions	12 months
RETRO	RCT	Haschka J et al., 2016	101	*Various*	NK	DAS28	48.1%	ACPA negative Lower baseline disease activity	12 months

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Study	Design	Authors	*n*	Treatment/Intervention *Drug Withdrawn in Italics*	RA Disease Duration	Remission Criteria	%DFR Remission in Biologic Treatment Arm	DFR Predicting Factors	Follow Up Period
								Male gender Lower multi-biomarker assay scores (serological) RF negative	
PredictRA	Double blind RCT	Emery et al., 2020	122	*Adalimumab taper* vs. *withdrawal*	Mean 12.9 years	DAS28	55% (withdrawal arm)	-	36 weeks
ANSWER	Cohort	Hashimoto et al., 2018	181	*Various*	NK	DAS28	21.5%	Boolean remission at baseline Sustained remission period No glucocorticoid use at time of discontinuation TNFi discontinuation (vs. other b-DMARD)	12 months

NK = not known.

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6. Predictors of DFR for Patients Receiving Treatment with b-DMARDs

6.1. Clinical and Demographic Variables

Although several potential biomarkers of b-DMARD-free remission have been reported, validated measures are yet to be identified. Shorter disease duration [46][47][48][49][50], fewer or absence of erosions [51][52] and low disease activity at baseline [46][53][54][55][56][57] have been consistently associated with successful discontinuation in several studies.

There is potential reversibility of autoimmunity in early disease. Subsequently, remission induction during this phase can increase the chance of successful b-DMARD discontinuation. This reversibility decreases with time, following which chronic synovitis ensues, in addition to persistent cytokine abnormalities, which can lead to structural progression. Thus, the efficacy of treatment may be reduced for patients with longer disease duration, resulting in only moderate clinical benefit and a reduced chance for DFR [58]. This concept is supported by the observation that treatment responses in the first 3 months following diagnosis can predict the later achievement of remission [59].

6.2. Patient Reported Outcomes (PRO) Measures

Lower PRO scores at baseline have been associated with a higher chance of successful maintenance of remission after b-DMARD withdrawal to achieve DFR. Good baseline functional status at ADA discontinuation (assessed by standardized patient questionnaires) has been shown to be predictive of low disease activity in the OPTIMA trial [60] and worsening functional disability has been shown to be associated with disease flare [19]. These findings are supported by the AVERT study [61], where lower baseline HAQ (health assessment questionnaire) was associated with successful DFR. The BeST study also found that lower HAQ score was associated with sustained DFR remission in their DAS-guided tapering cohort [39].

6.3. Imaging Variables

Musculoskeletal US has been shown to be a reliable method of predicting relapse in patients in clinical remission [62]; therefore, there is interest in using this tool to identify patients who may be able to taper or discontinue biologic therapy. Studies have revealed that the presence of synovitis (measured using power Doppler (PD) assessment) could predict failure of b-DMARD tapering for RA patients in clinical remission and that PD was a good predictor of disease flare within six months of tapering [63][64][65]. Additionally, grey-scale synovial hypertrophy (a measure of damage secondary to prior inflammation) is predictive of flare. Furthermore, El Miedany et al. [19] concluded that US was superior to DAS28 in predicting relapse for RA patients in remission, and both PD synovitis and synovial hypertrophy were independent predictors of relapse. Interestingly, Alivernini et al. [66] found that PD synovitis correlated with the histological characteristics of synovial tissue in established RA patients, thus suggesting that US, when combined with clinical remission criteria, could be a useful tool to identify patients likely to achieve DFR.

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6.4. Immunological Variables

To date, the best studied predictor of relapse on tapering/discontinuation of b-DMARDs is ACPA positivity. This indicated higher risk of relapse following dose reduction and lower chances of maintaining remission status [40][55][70][71]. IGM-RF was also associated with a reduced chance of TNFi-free remission [19][55][72][73][74].

Immune dysregulation is key to the pathogenesis of RA. Inflammation has a direct effect on T-cell differentiation and promotes the differentiation and proliferation of naïve CD4+ T-cells towards an abnormal phenotype. Characteristically, there is dysregulation of pro-inflammatory CD4+ T-helper cell subsets (naïve, regulatory (Treg) and inflammation-related cells (IRC)) [75][76]. Abnormalities in T-cell subsets have been found across the spectrum of RA and can predict progression, from ‘at-risk’ individuals to evolving RA and those in clinical remission [25]. In a study comparing the characteristics of 47 patients undergoing TNFi tapering, Saleem et al. [48] found that sustained remission was associated with T-cell subset immunological abnormalities. Patients who sustained remission for 24 months presented a higher frequency (%) of naïve T-cells and lower frequency of IRCs. Furthermore, the frequency of Treg cells was higher in the sustained remission group. These proportions were different for the patients receiving early, aggressive treatment compared to delayed treatment, for whom Treg frequency was higher.

6.5. Serum Biomarkers and Multi-Biomarker Assays

Multi-biomarker disease activity (MDBA) assays, developed to identify subclinical inflammation at the molecular level, have been investigated in several studies of RA patients in clinical remission. In general, studies have found that MDBA scores may be elevated in patients deemed to be in remission according to conventional clinical definitions [77][78][79][80]. These patients were also found to have a higher risk of structural joint damage [4][80].

One such score involves a total of 12 inflammation parameters, including markers linked to the acute phase [77]. It was initially developed and validated to correlate with the DAS28CRP score. Two studies have demonstrated that the score is better at predicting radiological progression than the DAS28CRP score [78][81]. In patients with high baseline MBDA scores at discontinuation of TNFi in the POET study, discontinuation may have allowed a recurrence of residual subclinical inflammation and the need to recommence TNFi treatment [50].

Collectively, these findings indicate that evaluating subclinical inflammation using serum biomarkers may be a useful tool to determine risk of flare/high risk candidates in whom tapering or discontinuation of therapy should not be initiated. Validation of this work is required.

6.6. Deep/Multi-Level Remission

As previously described, it is thought that achieving deep clinical remission is required to facilitate DFR [26].

Building on this, Gul et al. [82] aimed to define remission more precisely using a multi-dimensional model of remission using clinical, US and T-cell subset measures (for patients treated with either cs or b-DMARDs). In this cross-sectional study, considerable heterogeneity of DAS28 remission was observed with respect to these characteristics, with some patients showing evidence of high inflammatory markers and joint counts, evidence of synovitis on PD US and persistent T-cell subset abnormalities (which should not be present in remission). Definitions for clinical, US and T-cell subset remission were created and the achievement of all three was thought to represent a state of complete remission (multi-dimensional remission (MDR)). Out of approximately 200 patients, only 30% satisfied the criteria for MDR. These patients were found to have lower PRO scores. Further work has resulted in the development of a predictive model for successful tapering (towards DFR) of cs-DMARDs and work is underway to replicate this in a cohort of patients undergoing tapering and discontinuation of b-DMARDs [83]. This could help inform tapering strategies in clinical practice.