Chapter 9

Drug-free remission, is it already possible?

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ABSTRACT

Purpose of review To give an overview of recently published articles covering drug-free remission in rheumatoid arthritis.

Recent findings Recent studies covering drug-free remission showed differences in numbers studied, remission definition, disease duration and medication used. Drug-free remission was reported in 9-29%. Only 2/4 studies reported on patients who restarted medication due to a disease flare or loss of remission, which occurred in 45-46%. In the BeSt study, remission or low disease activity was achieved again after retreatment within 6 months in 96%. In the Finnish ERA study, none of the patients achieved remission after retreatment, their mean DAS28 was 3.68. Joint damage progression was not higher in patients who restarted medication when compared to patients in sustained drug-free remission or patients with continued treatment. ACPA, RF or SE negativity and short symptom duration were independent predictors of successful drug-free remission in more than 1 cohort.

Summary Drug-free remission can be achieved and sustained in a small group of RA patients. In early RA, retreatment is successful in the majority of patients. Disease flare after cessation of medication does not seem to increase joint damage progression. Sustained drug-free remission is predicted by auto-antibody and SE negativity and short disease duration before treatment initiation.

INTRODUCTION

Remission is the current treatment goal in rheumatoid arthritis.[1] Increasing numbers of patients in clinical trials achieve this goal.[2] This raises the question whether patients who have been in remission for a prolonged period still need medication. Although old studies have observed different remission rates in population-based RA and hospital based RA,[3] the current review has focused on hospital-based RA. Several small studies conducted in the 1970's and '80's show high relapse rates after cessation of Disease Modifying Anti-Rheumatic Drugs (DMARD),[4-8] with the exception of one trial in patients treated with high doses of gold.[9] In 1996, ten Wolde *et al.* published a double-blind placebo controlled study on 285 patients with longstanding RA in remission, who were randomized to continuing their DMARD, or to switch to placebo.[10] The sustained drug-free rate was 62% in 1 year in the drug-free (placebo) group. The BeSt study was the first large treatment strategy trial to show that in 65% of patients in remission, medication could be stopped without losing remission during median 11 months.[11] In this review, we discuss the most recent trials covering drug-free remission, radiological damage progression in drug-free patients, response after retreatment, and predictors of sustained drug-free remission.

Recent trials investigating drug-free remission

Predictors of sustained drug-free remission were studied[12] in the Leiden Early Arthritis Clinic (EAC) and the British Early Rheumatoid Arthritis Study (ERAS).(*table 1*) The follow-up duration of patients from these cohorts varied, with a maximum of 10 years. For the purpose of this study, drug-free remission in de EAC and ERAS was defined as having no swollen joints and drug-free remission according to the treating rheumatologist. The 454 patients from the Leiden EAC had RA according to the 1987 American Rheumatism Association (ARA, now ACR) diagnostic criteria at, or within one year after diagnosis. They were included between 1993 and 2002, and their mean symptom duration at inclusion was 6.4 months. Patients were either treated with analgesics, followed by hydroxychloroquine (HCQ) or sulfasalazine (SSA) in case of an insufficient response, or with initial HCQ, SSA or methotrexate (MTX), depending on their inclusion period. Sustained drug-free remission, defined as drug-free remission for at least 1 year consecutively, was achieved in 68/454 patients (15%). The 895 patients from the ERAS with recent onset RA according to the 1987 ARA criteria, were diagnosed slightly earlier, between 1986 and 1996. Their mean symptom duration at inclusion was 8.3 months. Patients were treated according to their rheumatologist's preference. Most patients were first treated with analgesics, followed by sequential monotherapy or combination therapy with synthetic DMARD in severe RA, in case of an insufficient response. Drug-free remission during at least 1 year was achieved in 84/895 patients (9.4%).

Table 1: studies covering drug-free remission published between June 2009 and December 2010

Reference (trial)	n follow-up complete	Inclusion*	Follow-up	Treatment	Cessation criteria	Retreatment criteria	n drug-free (%)	n sustained drug-free
Van der Woude et al (Leiden EAC)[12]	454/590	- Mean symptom duration 6.4 months - RA according to 1987 criteria at, or within 1 year after inclusion	Max 10 years	Analgesics, followed by synthetic DMARDs, or initial synthetic DMARD monotherapy	No swollen joints, remission according to rheumatologist	Retreatment not reported, sustained defined as ≥ 1 year		68/454 (15%)
Van der Woude et al (ERAS)[12]	895/1279	Mean symptom duration 8.3 months	Max 10 years	Analgesics, followed by sequential monotherapy or combination therapy in case of more severe RA, with synthetic DMARDs	No swollen joints, remission according to rheumatologist	Retreatment not reported, sustained defined as ≥ 1 year		84/895 (9%)
Tiipana-Kinnunen et al (Finnish ERA)[13]	70/87	Mean symptom duration 8 months	15 years	Sawtooth strategy with synthetic DMARDS, 4% treated with biologicals. Intramuscular glucocorticoids im and oral during active disease	1981 ACR remission criteria (14) excluding fatigue for ≥1year/ prolonged symptom free phase with minor disease activity	Disease flare	20/70 (29%)	11/70 (16%), of which 64% in remission at t=15 years
Hetland et al (CIMESTRA)[15]	139/160	- Median symptom duration 3.2 months in MTX+CSA group, 3.9 months in MTX+ placebo group - ≥2 swollen joints	5 years	Dynamic protocol: initial DMARD combination therapy vs initial monotherapy+placebo, + intraarticular glucocorticoids, see text	1981 ACR remission criteria ≥ 1 year	Retreatment not reported	17%	
Klarenbeek et al (BeSt)[16]	508 intention to treat analysis	Median symptom duration 23 weeks (≈ 5.8 months) - ≥ 6 swollen, ≥ 6 tender joints	5 years	Dynamic protocol aimed at DAS ≤2.4: Monotherapy or combination therapy with synthetic DMARDs, prednisolone, biologicals see text	DAS <1.6 for ≥ 6 months	Increase of DAS to ≥1.6	115/508 (23%)	59/508 (12%)

*Only patients with RA according to 1987 ARA criteria at diagnosis were included, unless stated otherwise

DMARD Disease Modifying Anti-Rheumatic Drug, ACR American College of Rheumatology DAS Disease activity score (53 tender, 44 swollen joints)

Drug-free remission and retreatment were studied in 70 Finnish early rheumatoid arthritis (ERA) patients,[13] in a prospective cohort study started in 1986 with a follow-up of 15 years. Median disease duration at inclusion was 8 months. Patients were treated according to the 'sawtooth treatment strategy'.

Most patients used conventional DMARD monotherapy and combination therapy in case of insufficient response, 4% used biologicals. DMARD were discontinued if remission according to the 1981 American College of Rheumatology (ACR) criteria[14] was achieved for at least 1 year, or in case of a prolonged symptom-free phase with minor disease activity. Nine (45%) out of the 20 patients who had been drug-free restarted treatment after a disease flare, after a median duration of 50 months. Of the 11 patients who had not restarted medication, 64% were in remission, the other 36% had low disease activity.

In the 5-year follow-up of the double-blind CIMESTRA trial, Hetland *et al*.[15] reported on the drug-free remission rate of 139 recent onset RA patients, included between 1999 and 2002. Patients were treated according to a dynamic treatment protocol. Initially, patients were randomized to receive either MTX+ciclosporin (CSA) or MTX+placebo. Both group received 2-weekly, and then monthly intraarticular bethamethasone injections in the first 52 weeks. HCQ was added after 68 weeks. After 2 years, MTX+CSA+HCQ triple therapy and then biologicals were started in case of insufficient response. The mean symptom duration at inclusion was 3.2 months in the combination therapy group and 3.9 months in the MTX+placebo group. After achieving remission according to the 1981 ACR criteria for at least 1 year, DMARDs were tapered and finally stopped. Drug-free remission at year 5 was achieved in 17% with no differences between the 2 initial treatment groups: 14% in the MTX+placebo group and 19% in the combination therapy group (p-value 0.68).

The most recent study on drug-free remission is the 5-year analysis of the 508 recent-onset RA patients from the double-blind BeSt trial, who were included between 2000 and 2002.[16] Median symptom duration at inclusion was 23 weeks (5.8 months). Patients were randomized in 4 treatment groups: sequential monotherapy, step-up combination therapy, initial combination therapy with prednisolone or initial combination therapy with a TNF- blocker (infliximab). Treatment was adjusted every three months in case of an insufficient response, differently for each treatment group. In group 1-3, combination therapy with a TNF-blocker was started after patients had failed on 3 previous treatment steps with synthetic DMARD including at some time prednisolone in groups 2 and 3. After a DAS (53/44 joint count) <1.6 on monotherapy was achieved for at least 6 months, medication was stopped. Drug-free remission was achieved in 115/508 patients (23%), with no significant differences between the four treatment groups. In 46%, DMARD had to be restarted due to a rise in disease activity to a DAS ≥1.6. The 51% in sustained drug-free remission had a median follow-up of 23 months after cessation of DMARD.

Response after retreatment

Clinical and radiological response in restarters was studied in two of the trials.(*table 2*) In the Finnish ERA study,[13] restarters had a significantly higher mean DAS28 at t=15 years than patients in sustained drug-free remission: 3.68 (SD 1.23) versus 2.08 (SD 1.01), with a p-value of 0.0018. The mean DAS28 in continued DMARD users was also slightly lower: 3.37 (SD 1.01). The mean scores on the Health Assessment Questionnaire (HAQ) of the three groups were not significantly different. Radiological damage after 15 years in restarters was also comparable to the other 2 groups. Restarters had a mean Larsen score of 25 (SD 30). There was a significant difference between continued DMARD users and patients in sustained drug-free remission. Their mean Larsen scores were 54 (SD 36) and 12 (SD 18), respectively, p<0.001.

In the BeSt study,[16] retreatment was successful in 96%: 25/53 patients achieved remission again within 3 months, 14/53 patients within 6 months, 11/53 achieved low disease activity. Two patients (4%) were lost to follow-up, 1 patient did not achieve low disease activity. The median HAQ scores of patients in drug-free remission and restarters were comparable to the scores of the general population. Significant radiological damage progression was not seen in the majority of drug-free patients in the first year after discontinuation of DMARD. Radiological damage progression in the first year of increase of disease activity in patients who needed retreatment was not different when compared to radiological damage progression in the first year after discontinuation of medication in patients in sustained drug-free remission. Median Sharp progression scores were 0 (IQR 0-1) and 0 (IQR 0-0) respectively, p-value 0.44.

Predictors

Although cessation of medication appears to be relatively safe with in general good response after retreatment and no increase in radiological damage progression, some patients don't achieve remission again after retreatment. Therefore, predictors of sustained drug-free remission are needed.

Van der Woude *et al*.[12] studied independent predictors of sustained drug-free remission, defined as drug-free remission for at least 1 year consecutively, in the Leiden EAC cohort and tried to replicate these results in the British ERAS cohort. The strongest predictor for sustained drug-free remission in the Leiden EAC cohort was anti-citrullinated protein antibody (ACPA) negativity, but ACPA status was not known for patients from the ERAS cohort. Rheumatoid factor (RF) negativity, Shared epitope (SE) negativity and short symptom duration at baseline were found to be independent predictors in both cohorts.(*table 2*)

A separate analysis of predictors of sustained drug-free remission was not described by Tiippana-Kinnunen *et al*.[13] in their Finnish ERA study. They did find an association with RF negativity and non-erosiveness at baseline and sustained drug-free remission.

Table 2: response after retreatment and predictors of sustained drug-free remission

Reference (trial)	Disease activity after retreatment	Radiographic damage	Predictors of sustained drug-free remission
Van der Woude (Leiden EAC and ERAS)	Not reported	Not reported	**Univariable**: RF, SE negativity, ACPA negativity in EAC, acute onset of symptoms, baseline low disease activity and low HAQ in ERAS **Independent predictors**: short symptom duration, low baseline CRP and ACPA negativity, or short symptom duration, RF negativity and SE negativity
Tiippana-Kinnunen (Finnish ERA)	Mean DAS28 at t=15 years 3.68 (SD 1.23), 0% remission, mean HAQ 0.38 (SD 0.51)	Mean Larsen scores at t=15 years: Continuous treatment group: 54 (36) Restarters: 25 (30) Successful drug-free group: 12 (18), p<0.001	Association with RF negativity, non-erosiveness
Klarenbeek (BeSt)	96% good response: 47% again clinical remission within 3 months, plus 26% after 6 months, 21% again low disease activity, median HAQ 0.20 (IQR 0.15-0.34)	Median increase in Sharp van der Heijde scores after 1 year drug-free: Restarters 0 (IQR 0-1) Sustained drug-free: 0 (IQR 0-0) p=0.44	**Univariable**: ACPA/RF negativity, higher HAQ at baseline, higher VAS global health at baseline **Independent predictors**: ACPA negativity, lower disease activity until remission, higher baseline HAQ, MTX compared to SSA as last DMARD before drug-free remission

ACPA Anti citrullinated protein antibodies *RF* Rheumatoid factor *SE* Shared epitope *DAS* Disease Activity Score *HAQ* Health Assessment Questionnaire *VAS* Visual analogue scale *SSA* Sulfasalazine *MTX* Methotrexate *DMARD* Disease Modifying Anti-Rheumatic Drug

ACPA negativity was also found to be the strongest predictor of sustained remission in the BeSt study,[16] followed by low DAS until remission, a higher baseline HAQ and SSA as last DMARD when compared to MTX. RF negativity was associated with sustained drug-free remission in the univariable analyses.

In summary, all trials found RF negativity to be associated with sustained drug-free remission. ACPA negativity was found to be an even stronger predictor in those cohorts that measured ACPA status. Short symptom duration before treatment initiation and SE negativity predicted sustained drug-free remission in two cohorts.

Translation to clinical practice and consequences for further research

The four recent studies on drug-free remission cover a heterogeneous patient population, treated according to different strategies. Different remission definitions and criteria for retreatment were used. The available sets of remission criteria vary in components used and in stringency.(*table 3*)

It is therefore hard to draw general conclusions. These recent studies and previous publications do show that drug-free remission is indeed possible in 17-29% of patients. Sustained (>1 year) remission was reported in an even smaller group: 9-16% of all patients. Retreatment was needed in 44-45% of all drug-free patients in recent studies[13,16] and in 11-100% of all drug-free patients in older publications.[4-6,17] More research on sustainable drug-free remission is necessary, with longer follow-up. Preferably, these studies would use a uniform set of remission criteria. Recently, new criteria have been proposed by the ACR/EULAR Commission to Redefine Remission in Rheumatoid Arthritis.[18] In contrast to the ACR 1981 criteria, these criteria allow for 1 swollen and 1 tender joint. This does raise the concern that patients in remission might still have active synovitis, causing joint damage.[2] Only two of the 115 patients in DAS remission (which shows similarities with the new criteria (*table 3*)) from the BeSt study, showed clinically relevant joint damage progression in the first year after cessation. Unfortunately, long-term radiologic follow-up of patients in drug-free remission is not yet available. This underlines the importance of monitoring of disease activity and joint damage progression in patients in drug-free remission. Future research should also focus on radiological joint progression in drug-free patients with longer follow-up duration. Secondly, one wonders if patients who have discontinued all anti-rheumatic drugs can taper or need to intensify other therapies such as NSAIDs or physical therapy, but none of the papers offer information on that.

Furthermore, only few studies report on the effect of retreatment: do patients respond well to therapy again? The positive results from the BeSt study, which included 508 patients, and had a dynamic treatment protocol in which treatment effect was evaluated every three months, suggest that this is indeed the case. Retreatment was successful in 96%. DMARD were stopped when patients were in DAS-remission for at least 6 months and restarted when remission was lost. These results are in line with some smaller studies conducted between 1976 and 1987 investigating cessation of and retreatment with synthetic DMARD[4,5,7] and a more recent trial which studied cessation of and retreatment with biologicals,[19] which all report a good response after retreatment in all patients. However, in the study of ten Wolde *et al*., only 78% had a good response to retreatment[20] and in the Finnish ERA trial, the majority of patients did not achieve low disease activity during follow up after retreatment. A possible explanation for these differences is that in these studies, treatment was restarted when disease flared to moderate or high disease activity, where in the BeSt study patients were retreated when an increase in DAS to >1.6 occurred. Secondly, not all patients in the Finnish trial were in clinical remission when medication was stopped. These results suggest that DMARD should only be stopped in patients in sustained clinical remission. Treatment should be restarted as soon as remission is lost, without delay.

Table 3: comparison of remission criteria

Criteria or composite index (14;17)	ACR 1981 criteria	Modified ACR criteria	FDA criteria	Preliminary new ACR remission criteria	DAS<1.6*	DAS28<2.6*	SDAI ≤3.3	CDAI ≤2.8
Total of swollen & tender joints**	0	0	0	≤1/28 swollen and ≤1/28 tender	≤1/44 swollen and ≤1/53 tender	≤1/28 swollen or ≤1/28 tender	0/28 swollen, 0/28 tender	0/28 swollen, 0/28 tender
Systemic inflammation	ESR <30 mm/h female, <20 mm/h male	ESR <30 mm/h female, <20 mm/h male	ESR <30 mm/h female, <20 mm/h male	CRP ≤1	ESR or CRP	ESR or CRP	CRP	
Other criteria	1. Duration of morning stiffness ≤15 min 2. No fatigue 3. No tenderness or pain in motion 4. No tendon sheet swelling	1. Duration of morning stiffness ≤15 min 2. Pain (VAS) ≤1cm 3. No tendon sheet swelling	1. ACR 1981 criteria 2. No DMARDs 3. Radiographic arrest (Larsen or Sharp) ≥6 months	1. Patient global assessment (VAS) ≤1 cm	1. Patient's assessment of global health (VAS)	1. Patient's assessment of global health (VAS)	1,2. Patient's and evaluator's assessment of disease activity (VAS)	1,2.Patient's and evaluator's assessment of disease activity (VAS)

ACR American College of Rheumatology, *FDA* US Food and Drug Administration, *DAS* Disease Activity Score, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-reactive protein, *VAS* visual analogue scale

*Calculated with CRP for comparison with SDAI and CDAI. Hypothetically, for patients in DAS remission a larger number of swollen joints would be possible if these were not tender.

**For composite indices: calculated assuming CRP =1 mg/dL, VAS scores= 1cm

CONCLUSION

There are few studies that report on drug free remission in RA and even fewer that report on restart of treatment. From 4 recent studies in patients with recent onset RA with a follow-up duration up to 15 years, the following conclusions can be drawn:

- Drug-free remission is achieved in 17-29% of patients and sustained in 9-16% during 1-4 years.
- Joint damage progression in drug-free patients is not different from DMARD users and does not increase in the first year(s) of drug-free remission, regardless of flare.
- Low disease activity is achieved again in the majority of patients who have to restart treatment.
- Auto antibody negativity (RF, ACPA), shared epitope negativity and short symptom duration before treatment initiation are predictors of sustained drug-free remission.

The low rates of drug-free remission are possibly due to the fact that the treatment of these patients was aimed at achieving low disease activity, at best. With new treatment options more patients can now be treated to achieve remission, and potentially this will lead to more drug free remission in the future. Clinical research should focus on the consequences of drug-free remission and retreatment after longer-follow up and on identifying predictors of sustained drug-free remission.

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