Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis?

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ABSTRACT

After achieving low disease activity or remission, biological therapy might be stopped in rheumatoid arthritis patients, but information on whether and how this should be done is scarce. Successful discontinuation was highly variable since it was described in 0-97% of patients, in studies with different patient populations and follow-up durations between 12 weeks and over 7 years. In most studies, patients were required to have low disease activity or be in clinical remission for at least 6 months before biological therapy was discontinued. Significant joint damage progression in the first year after discontinuation was rare and functional ability was relatively stable in almost all patients in this year. In patients who had a disease flare, retreatment with biological therapy was successful in 70–100%. Mild infusion reactions after retreatment were described in a small number of patients. In conclusion, in the absence of a guideline for stopping biologicals in RA, we present a preliminary proposal that biological therapy can be stopped in many RA-patients after achieving low disease activity or remission for at least 6 months. Adequate monitoring of disease activity is essential, and retreatment appears to be safe and successful in many patients. Future research may further identify when and/or which patients are most likely to discontinue biological treatment successfully.

Introduction

Achieving low disease activity or remission in order to maintain functional ability and prevent joint damage is the treatment goal of rheumatoid arthritis (1). There is evidence that treatment with methotrexate in combination with a biological agent results in more remission than treatment with methotrexate monotherapy (2). On the other hand, biological therapies increase the risk of infections, have the potential downside of parenteral administration and have a high cost. If they are not essential to maintain suppression of rheumatoid inflammation, it would be beneficial if such therapies could be discontinued once the initial treatment goal has been achieved. There are guidelines on how to start and adjust biological therapy (1, 3), but information on if and how biological therapies can be stopped is scarce.

Can biologicals be stopped?

In addition to some case studies of biological discontinuation at the conclusion of a clinical trial (4, 5), several clinical trials have included discontinuation of biologicals and subsequent follow up in their design. Patients who had a good response to biological treatment, by various definitions, were eligible for biological discontinuation (Table I).

Consequences of discontinuation

All 17 patients who had to discontinue infliximab at the end of the ATTRACT trial, and all 4 patients who had to discontinue tocilizumab at the end of the SAMURAI trial, flared (4, 5). Discontinuation of TNF-inhibitors resulted in disease flare in between 22% and 71% of patients in 3 other small trials (6, 7, 8). In the BeSt study and the RRR study, just over 50% of patients had a disease flare after discontinuation of infliximab (9-11). Discontinuation of adalimumab as part of the HONOR and OPTIMA study was followed by loss of clinical remission (HONOR) or low disease activity (OPTIMA) in 43% and 19%, respectively (12, 13). In the HIT HARD study, adalimumab was stopped in all patients after 24 weeks; 44% were still in remission after 24 weeks of follow-up, compared to 47% at discontinuation (14). Subcutaneous abatacept was discontinued after DAS improvement

Table I. Overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients.

Study	Patients	Treatment	Withdrawal	Follow-up period	Biological-free	Results	Predictors of relapse	Result of retreatment
ATTRACT 2004 (4)	1987 RA, active disease despite methotrexate, n=17 (all trial patients from Leeds who entered the extension phase)	*Infliximab* 3 or 10 mg/kg per 4 or 8 weeks+ methotrexate (corticosteroid allowed)	In all patients at t=24 months	9 months	Methotrexate (corticosteroid allowed)	*DAS: 17/17 flared* within 15 weeks *HAQ:* no data *Radiology:* no data	No data	15/17 retreated: no infusion reactions or toxicity, 12/15 good ACR respone, 2 not, 1 stop (pregnancy wish)
Quinn 2005 (7)	Early RA (<1yr), no previous DMARD or corticosteroid, n=10	*Infliximab* 3 mg/kg+ methotrexate, 1 pt only 1 infusion of infliximab	In all patients at t=54 weeks (last dose t=46 weeks) (9 had good response, 1 did not)	1 year	Treatment according to rheumatologist's preference	*DAS: 2/9 flared* ≥32 weeks after last infusion: increase in DAS28 *HAQ:* no detoriation of functional ability *Radiology:* no data	No data	No retreatment
Brocq 2009 (6)	987 RA patients using 1 anti-TNF, not a history of relapsing after discontinuation of anti-TNF, n=21	*Infliximab* (n=2) 3mg/kg, *etanercept* 50 mg/week (n=7)/25mg/week (n=7) or *adalimumab* 40 mg/2 weeks (n=4)/40mg/3 weeks (n=1), stable DMARD and corticosteroid dose (≤5mg) for 6 months	If *DAS28 <2.6* for ≥6 months and biological on maintenance dose or lower,	1 year	DMARD (and corticosteroid) on a stable dose, 5 drug-free	*DAS: 15/21 flared*, 1 died, of the 5 relapse free, 2 were drug-free, of the 4/15 who relapsed had been drug-free *HAQ:* no data *Radiology:* in relapse free patients: 4 no progression, progression of a pre-existing 1 erosion	Shorter treatment duration with anti-TNF, shorter mean time in remission, male gender, RF negativity	13/15 remission within 2 months, 2/15 remission after 4 and 5 months: 100% again remission No adverse events
RRR 2010 (9)	RA 1987, not achieving LDA on methotrexate 3 months n=114	*Infliximab* 3mg/kg (possibly in some patients with methotrexate, unclear)	If *DAS28 <3.2* for 24 weeks, concomitant methotrexate started,	1 year	Methotrexate, <5 mg prednisone, prednisone could be tapered	*DAS: 46/102 flared* (DAS28 ≥3.2), 12 withdrew *HAQ:* 0.2 for relapse-free, 0.6 for relapse *Radiology:* data from 49/114: 22/33 relapse free and 7/16 with relapse deltaSHS<0.5, median progression 0.0 *vs*. 1.5	High (>2.2) DAS28 at cessation	32/46 effective retreatment. Minimal infusion reaction in 5/46
Saleem 2010 (8)	1987 RA n=47	*TNF-blocker* + methotrexate: 27 initial combination therapy, 10 failed ≥ 2 DMARD, 10 failed ≥ 2 DMARD and a TNF blocker	If *DAS28 <2.6* on stable therapy for ≥6 months,	1 year	Methotrexate	*DAS: 28/47 flared* (DAS28≥2.6) *HAQ:* no data *Radiology:* no data	Longer disease duration, higher HAQ at cessation, higher RAQoL at cessation, longer symptom duration before starting any treatment, delayed treatment? Multivariate, in initial treatment group: symptom duration at start of first treatment, high inflammation related cell frequency, high regulatory T cell frequency, low proportion of naïve T-cells	No data

Study	Patients	Treatment	Withdrawal	Follow-up period	Biological-free	Results	Predictors of relapse	Result of retreatment
ALLOW 2011 (15)	1987 RA, high disease activity, using methotrexate for 3 months prior to study period, 10% had used previous biological, n=80	*Abatacept* + methotrexate 12 weeks	In all patients with ΔDAS28 ≥6 after 12 weeks, retreatment after 12 weeks or if flare,	12 weeks	Methotrexate stable dose + placebo + in 55% low dose prednisone (<10 mg), 1 patient high dose	*DAS:* mean DAS28 increase 0.39, *2/80 flared* before end of 12-week period because of lack of efficacy *HAQ:* no data *Radiology:* no data	No data	7/73 antibodies vs 0/38 in continued abatacept group No injection site reactions or other injection related AE's
BeSt 2011 (10)	1987 active RA, n=104	Initial (n=77) and delayed (n=27) *infliximab* with dose escalation when needed plus methotrexate	DAS44≤2.4 for ≥6 months on infliximab 3mg/kg, mean	7.2 years	Methotrexate monotherapy, dose escalation when needed, tapering when continued remission	*DAS: 50/104 flared* *HAQ:* 5 years after cessation: HAQ 0.7 *vs* 0.3 at cessation in restarters, patients who did not flare continued to have a HAQ of 0.1 *Radiology:* Median damage progression 0 in year after cessation, 4 patients progression>5 (1 flared)	Smoking, long time to achieve low disease activity on treatment, presence of HLA shared epitope, delayed treatment?	42/50 good response, 2/50 not (yet), 6 patients stop, 5/50 mild infusion reaction
HIT HARD 2011 (14)	Active RA n=87	Adalimumab 40mg/2 weeks plus methotrexate s.c. 15mg/week	Withdrawal after 24 weeks in all patients,	24 weeks	Methotrexate monotherapy s.c. 15mg/week	*DAS:* mean DAS28 increase 0.2 points, 47% had remission, 3% lost remission *HAQ:* mean HAQ increase 0.11 points *Radiology:* no specific data	No data	No data
OPTIMA 2011 (12)	Active RA, n=102	Adalimumab plus methotrexate for 26 weeks	Stable low disease activity (DAS28),	52 weeks	Methotrexate plus placebo	*DAS:* 19% lost low disease activity *HAQ:* mean HAQ 52 weeks after discontinuation 0.35 *Radiology:* no specific data	High HAQ at baseline	No data
HONOR 2011 (13)	Active RA, n=30	Adalimumab plus methotrexate, ≤5 mg steroids per day	Das28< 2.6 for >24 weeks,	6 months	Methotrexate	*DAS:* 43% lost remission, 27% high disease activity *HAQ:* no data *Radiology:* at t=1 year in 17 patients[a]: change in mean SHS -0.2 for patients in continued remission, 1.9 for patients who flared (n=7)	DAS28 >1.9 at discontinuation	No data

>0.6 in the ALLOW study, followed by a disease flare in 3% in the next 3 months (15). In all cases of biological discontinuation, comedication with methotrexate or other disease modifying anti-rheumatic drugs was initially continued (Table I).

Biological therapy is very effective in suppressing joint damage, possibly even when there are still symptoms of inflammation (16). Brocq *et al*. showed that 4/5 of the patients who did not show a relapse also showed no radiological progression, while one patient showed erosion progression only in 1 joint (6). In the RRR study, no progression was seen in 22/33 relapse-free patients and in 7/16 who did have a relapse (9). On a group level there was no significant progression in either group: they had a median change in Sharp / vd Heijde score (SHS) of 0.0 and 1.5 respectively a year after discontinuation. In the BeSt study, median damage progression in the year after discontinuation was 0 as well (10). Damage progression >5 point SHS occurred in 4 patients, one of whom had relapsed and restarted infliximab in that year. In the HONOR study, mean damage progression (SHS) 1 year after discontinuation was -0.2 in the 10 patients with radiological data who were still in remission, and 1.9 in the 7 patients who flared (13).

From a patient point of view, minimal radiological damage progression is irrelevant if it does not influence functional ability. None of the 9 patients in Quinn's study who discontinued infliximab showed detoriation of functional ability (7). In the RRR study, the median Health Assessment Questionnaire (HAQ) score was 0.2 in the relapse-free group and 0.6 in the relapse group (9). In the BeSt study, no difference in functional ability was seen 1 and 3 years after discontinuation of infliximab, irrespective of whether biological therapy had to be restarted. However, after 5 years, patients who had restarted infliximab did show a slight deterioration of functional ability: HAQ score changed from 0.3 to 0.7 (10). In the OPTIMA study, the mean HAQ score a year after discontinuation was not different from the HAQ in the group that had continued adalimumab (12). The patients from the HIT HARD study showed a rise in mean HAQ of 0.11 points 24 weeks after discontinuation (14).

Retreatment

Reintroduction of biological therapy was successful in 85–100% of the patients of the ATTRACT study, BeSt study, the study by Brocq *et al*. and the patients who restarted tocilizumab after the SAMURAI study (4-6, 10). In the RRR study, retreatment was effective in 32/46 (70%) patients (9). No adverse events or infusion/injection site reactions were described in the ATTRACT study, the ALLOW study or the study by Brocq *et al*. Mild infusion reactions occurred in 2/4 retreated patients (who had a history of drug hypersensitivity) in the SAMURAI study, 5/50 retreated patients in the BeSt study and in 5/46 patients in the RRR study (5, 9, 10). In the BeSt study, this was compared to the number of infusion reactions in patients first treated with infliximab and no significant differences were found, indicating that retreatment did not seem to increase the risk of infusion reactions. The ALLOW study was the only study in which antibodies to the biological therapy were measured. They were found in 7/73 patients who had discontinued abatacept for 3 months, compared to none of the 38 patients who had continued abatacept. Response to therapy did not seem to be influenced by these antibodies, as disease activity 12 weeks after reintroduction of abatacept was similar to disease activity in the group with continued treatment.

Discontinuation strategies

In the 2010 EULAR recommendations it is stated that it is currently unclear how to discontinue treatment in patients who have achieved remission (1). It is advised to consider slow tapering of biological therapy only in patients who have been in 'persistent remission' and only after glucocorticoids have been tapered first. According to expert opinion, persistent remission should be defined as remission for at least 12 months. There are few studies that include systematical long term follow up of patients who achieve clinical remission.

As described in Table I, most studies have discontinued biological treatment at higher levels of disease activity and earlier. It may be that fewer patients would relapse if long term remission was maintained before discontinuation. On the other hand, if strategies are in place to detect an increase in disease activity early and restart treatment immediately, it may be acceptable to aim at a temporary drug holiday rather than permanent drug free remission. To spare patients the most severe flares, it would help to be able to identify which patients are likely to discontinue biologicals successfully.

Predictors of successful discontinuation

The reported predictors of successful discontinuation differ per study. Saleem *et al*. found shorter disease duration, better functional ability at discontinuation and shorter symptom duration before starting any treatment to be predictive of successful discontinuation. Brocq *et al*. found that patients who were male, rheumatoid factor negative, had longer biological treatment duration, and/or a longer mean time in remission less often had to restart biological therapy. The RRR study and the HONOR study found that patients who had a low DAS28 (≤2.2 and ≤1.9 respectively) at discontinuation were least likely to have to restart treatment. In the HONOR study, patients with a low HAQ before starting treatment had to restart less often. In the BeSt study, rapid achievement of low disease activity on infliximab, non-smoking and absence of HLA shared epitope were independent predictors of successful discontinuation. There is a suggestion that initial treatment with biologicals results in more successful discontinuation than delayed treatment, but this may at least in part be explained by selection bias.

Do we need discontinuation guidelines?

From these studies we can conclude that in patients who have been in prolonged (at least 6 months) low disease activity or remission, discontinuation of biological therapies is an appropriate option. In the short term, this will

have no consequences for radiological damage progression or functional ability in the majority of patients (6, 8, 9, 10). If disease activity increases and patients need retreatment, this seems to be safe and effective, although in the RRR study and in long term follow-up in the BeSt study, some patients who had to be retreated had a small increase in HAQ score.

Outside of clinical trials, reports of discontinuation of biological agents other than because of side effects, contraindications or failure to respond are scarce. Recently, van der Maas *et al*. described an observational cohort in which down-titration of infliximab in patients with a DAS28<3.2 led to infliximab-free low disease activity in 8/51 patients (17). No follow-up of these patients was described.

There may a discrepancy between findings in clinical trials and experience in daily practice. The patient populations may differ, as well as patients' and physicians' expectations about treatment (dis)continuation. Most patients on biologicals outside clinical trials have started those treatments only after prolonged high disease activity and failure on other drugs. One can understand that they would be anxious not to risk a relapse. On the other hand, serious complications during treatment with biologicals may occur in some patients, and unnecessary continuation of such drugs therefore is unwise.

In some countries, patients must pay for part or all of the medication costs themselves. Although this may cause delays in treatment initiation, it also results in more patients willing to discontinue when it appears safe.

The clinical trials have shown that for some patients at least, rheumatoid arthritis is not so much a chronic disease that needs constant suppression with immunomodulating drugs, but rather a disease that requires a strategy of induction and consolidation therapy, followed by tapering and discontinuation of medication. It is obvious that relapses can happen, and we need monitoring strategies with scoring of disease activity to ensure that rapid, and perhaps again temporary, treatment is restarted. Future research should focus on identifying patients most at risk for relapsing who need the most intensive monitoring, optimising the monitoring strategy itself (frequency, possible contributions of imaging techniques and biomarkers if the usual composite scores are insufficient or impractical), and on optimising the induction and consolidation therapies (timing, choice of drugs, treatment target, continuation of comedication). In addition to longer follow-up data from clinical trials, daily practice based observational studies with sufficiently long and systematic follow up are also needed. Patients' expectations and wishes should be incorporated in such research. Administrators will require real time cost-utility analyses.

In conclusion, it seems too early to provide detailed guidelines for discontinuation of biologicals, but we would like to propose three recommendations. Recommendation 1: if patients have had low disease activity or been in remission for at least 6 months, consider trying it! Discontinuation of biological therapy has been shown to be possible for at least 1 year in 29-80% of patients who had had low disease activity or been in remission for at least 6 months. Recommendation 2: once biologicals are discontinued, as ever, keep monitoring disease activity, functional ability and radiological damage progression. During the year following biological discontinuation, radiological damage progression was rare and functional ability was maintained in the majority of patients. But a deterioration in either of those would suggest to follow up with recommendation 3: restart treatment as soon as it appears that the disease is relapsing. Retreatment was effective in 70–100% of patients. Infusion reactions after retreatment with infliximab were mild and in a low frequency comparable to that observed during initial infliximab treatment. We look forward to reports on such projects.

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