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LEADING ARTICLE

Intensive Intervention Can Lead to a Treatment Holiday from Biological DMARDs in Patients with Rheumatoid Arthritis

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Abstract Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction that causes significant morbidity and mortality. However, the combined use of methotrexate (MTX), a synthetic disease-modifying anti-rheumatic drug (sDMARD) and biological DMARDs (bDMARDs) has revolutionized treatment of RA and clinical remission or low disease activity (LDA) are now realistic targets, achieved by a large proportion of RA patients. We are now in a position to evaluate if it is possible to maintain remission or LDA while at the same time reducing the burden of treatment on the patient and healthcare system. Data are emerging from large, well-conducted studies designed to answer this question, shedding light on which patient populations and treatment algorithms can survive treatment discontinuation or tapering with low risk of disease flare. For early RA, approximately half of early RA patients could discontinue TNF-targeted bDMARDs without clinical flare and functional impairment after obtaining clinical remission by bDMARDs with MTX. In contrast, for established RA, fewer patients sustained remission or LDA after the discontinuation of bDMARDs and "deep remission" at the discontinuation was a key factor to maintain the treatment holiday of bDMARDs. Thus, this article provides a brief outline on withdrawing or tapering bDMARDs once patients have achieved remission or LDA in RA.

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Key Points

The discontinuation of biological disease-modifying anti-rheumatic drugs (bDMARDs) is possible without clinical flare and functional impairment for early rheumatoid arthritis (RA) patients with low disease activity or remission.

For patients with established RA, "deep remission" at the time of discontinuation is required to maintain the treatment holiday from bDMARDs.

"Treatment holiday" from bDMARDS following early intensive treatment may be beneficial for reduction of drug-induced adverse effects and costs.

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, leading to synovial hypertrophy and adjacent bone and cartilage destruction. However, the combined use of methotrexate (MTX), a standard synthetic disease-modifying anti-rheumatic drug (sDMARD) and a biological DMARD (bDMARD) has revolutionized treatment of RA and clinical remission or low disease activity (LDA) are now realistic targets, achieved by a large proportion of RA patients. Currently, discontinuation of a bDMARD without disease flare is our next goal and desirable from the standpoint of risk reduction and cost effectiveness, especially for patients with clinical remission or LDA. Data are emerging from large, well-conducted studies designed to answer this question, shedding light on which patient populations and treatment strategies can survive treatment

discontinuation or tapering with low risk of disease flare [1–5]. The goal of the present Leading article is to determine if discontinuation of a bDMARD is possible in RA patients, after obtaining LDA or clinical remission by the use of bDMARDs. The content is based on results of a systematic literature review as well as new information.

2 Systematic Literature Search Regarding Discontinuation of Biological DMARDs (bDMARDs)

First of all, a search of PubMed using a search strategy that combined terms for "rheumatoid arthritis", "biological agent" and "discontinuation, discontinuing or cessation" was performed as below:

#1. rheumatoid arthritis
#2. discontinuation OR discontinuing OR stop OR stopping OR cessation OR withdrawal
#3. biological dmards OR biological drugs OR anti-tnf OR tnf inhibitor OR infliximab OR remicade OR etanercept OR enbrel OR adalimumab OR humira OR tocilizumab OR actemra OR roactemra OR abatacept OR orencia OR golimumab OR simponi OR certolizumab OR cimzia OR rituximab OR rituxan
#4. remission OR low disease activity
#5. English[Language]
#6. arthritis, juvenile rheumatoid[MeSH]
#7. review[Filter]
#8. #1 AND #2 AND #3 AND #4 AND #5 NOT #6 NOT #7

During screening the titles and abstracts of the citations and retrieved relevant articles, the following selection criteria were used; (a) clinical trials of bDMARDs in patients with RA, followed by discontinuation of a bDMARD due to preferable effectiveness but not to adverse events nor to insufficient efficacy, (b) patients with RA >18 years old, (c) data available on one or more of following pre-specified outcomes: proportion of remission or low disease activity after at least 12 weeks of discontinuation and/or proportion of re-administration of a bDMARDs (d) published after 1998 that the first bDMARD to be available.

By performing a PubMed search on July 5th, 2014, 86 original research articles were found. Then systematic literature review revealed that 19 articles were as candidate studies, and 67 articles were excluded. The reasons for exclusion were categorized into three groups; (1) No description of discontinuing biologics, (2) Reasons for discontinuing biologics are not specified, (3) No description of discontinuing biologics due to preferable effectiveness. We also added the abstracts search on the American College of Rheumatology (ACR) 2011, 2012, 2013, the European League against Rheumatism (EULAR) 2012, 2013, 2014, and finally identified 26 reports as the candidate studies, summarized in Table 1.

3 Stopping a bDMARD in Established RA

There is little information about characteristics of patients in which a bDMARD is successfully discontinued without functional and radiographic damage progression in patients with long-term established RA encountered during routine clinical practice.

3.1 RRR Study

We first reported a RRR study aimed at the possibility of biologic-free remission in RA patients whose mean disease duration was 5.9 years [6]. This study included a total of 114 patients, from 26 centers, with RA who reached and maintained LDA (disease activity score 28; DAS28 <3.2) for more than 24 weeks with infliximab treatment. Among the 102 evaluable patients who completed the study, 56 and 44 maintained LDA and remission (DAS28 <2.6), respectively, after 1 year and showed no changes in radiological damage measured by yearly progression of modified total Sharp score (mTSS) and functional disturbance measured by health assessment questionnaire-disability index (HAQ-DI) score. By logistic regression and a receiver-operating characteristic curve (ROC) analysis, the cut-off point for achieving RRR at the time of patient enrollment was a DAS28 of 2.22, and a 'deep' remission was necessary at the time of the discontinuation. The study demonstrated that 71.4 % patients with deep remission (DAS28 ≤2.22) were able to continue LDA for 1 year, whereas only 32.6 % patients with a DAS28 score of between 2.22 and 3.2 were able to continue LDA, suggesting that established RA patients in deep remission have a possibility to achieve biologic-free remission.

3.2 HONOR Study

We also carried HONOR study to investigate the possibility of discontinuing adalimumab for 1 year without flaring measured by DAS28-ESR ≥3.2 in RA patients [7, 8]. Prior to the study, 197 RA patients with inadequate response to MTX were treated with MTX and adalimumab and 75 patients met the adalimumab-free criteria (steroid-free and sustained DAS28-ESR remission for more than 6 months). The mean disease duration and DAS28-ESR score in 75 patients was 7.5 years and 5.1 at baseline, respectively. Of the 75 patients, 52 (69 %) agreed to adalimumab discontinuation and 23 patients continued to use adalimumab for 1 year. The remission rate (83 %) and the

Table 1 Summary of the candidate studies evaluating discontinuation of biologics in rheumatoid arthritis

	Author study name Country	Targeted discontinuing drug	Concomitant DMARDs	Symptom duration	Criteria for discontinuation	Follow up period	Number/of patients with discontinuation	Ratio of and time to restart/failed	Effect of restart	Predictors of successful discontinuation
1	Quinn TNF20 UK [17]	Infliximab	MTX	6 mo (mean)	No criteria for cessation of IFX. MTX + IFX/PBO for 1 y, followed by MTX monotherapy.	1 y after discontinuing IFX (total 2 y)	10 discontinued IFX	30 %, DAS28 = 2.05 (mean) at 1 y after stopping IFX	Not specified	Not described
2	van der Bijl BeSt Netherlands [20]	Infliximab	MTX up to 25 mg	23 wks (median)	DAS ≤2.4 ≥6 mo	2 years of study protocol	56 % (67/120), median 9.9 mo, median MTX 10 mg	15 % (10/67) restarted IFX at 3.7 mo (median) after cessation	Not specified	See #9
3	Nawata (case series) Japan [31]	Infliximab	MTX	28.7 mo (mean)	Inclusion: DAS28-ESR < 2.6 ≥ 24wks Exclusion: not specified	Not specified	5 % (9/172)	Restarted/failed is unclear 14.2 mo (mean) 29 mo (longest)	Not specified	Not described
4	Brocq France [32]	Infliximab Adalimumab Etanercept	DMARD	11.3 y (mean)	DAS28 < 2.6 for at least 6 mo without NSAIDs or PSL >5 mg	12 mo	6.9 % (21/304) IFX 2 ADA 5 ETN 14	55 % (11/20) at 6 mo, 75 % (15/20) at 12 mo failed from DAS28 <2.6	87 % (13/15) achieved DAS28 <2.6 within 2 mo	See #9
5	van der Kooij BeSt Netherlands [21]	Infliximab	MTX	23 wks (median)	DAS ≤2.4 ≥6 mo	2 y after IFX initiation	56 % (66/117) in initial IFX group 29 % (19/67) in delayed IFX group	Not specified	Not specified	See #9
6	Tanaka RRR Japan [6]	Infliximab	MTX	5.9 y (mean)	DAS28-ESR ≤3.2 > 24 wks	1 y after IFX discontinued	114 discontinued IFX, 102 evaluated at 1-y	46/102 (45 %) failed	Not specified	DAS28 ≤2.225 at discontinuation
7	Bejarano TNF20 UK [18]	Infliximab	MTX	6.5 mo (mean)	No criteria for cessation of IFX. MTX + IFX/PBO for 1 y, followed by MTX monotherapy	8 y after discontinuing IFX	10 discontinued IFX (1 died and 9 available). 4/9 kept remission 1/4 drug free	5/9 (56 %) failed	Not specified	Not described
8	Klarenbeek BeSt Netherlands [22]	Last DMARD Including pts after cessation of IFX	BeSt study arms	23 wks (median)	DAS ≤1.6 ≥6 mo	5 y after study protocol	115/508 (23 %): drug-free	53/115 (46 %) restarted IFX at 23 mo (median)	39/53 (74 %) DAS ≤1.6	See #9

Table 1 continued

	Authorstudy nameCountry	Targeted discontinuing drug	Concomitant DMARDs	Symptom duration	Criteria for discontinuation	Follow up period	Number/of patients with discontinuation	Ratio of and time to restart/failed	Effect of restart	Predictors of successful discontinuation
9	van den Broek BeSt Netherlands [23]	Infliximab	BeSt study arms	23 wks (median)	DAS ≤ 2.4 6 mo	7.2 y after discontinuation (median)	27/109 in delayed IFX group, 77/120 Initial IFX group discontinued IFX	48 % restarted IFX at 17 mo (median)	84 % DAS ≤ 2.4	Smoking, IFX treatment duration ≥18 mo, shared epitope
10	Harigai BRIGHT Japan [10]	Adalimumab	None (ADA monotherapy)	10.3 years (mean)	DAS28-CRP <2.7 at last the last administration of ADA Duration not specified	52 wks	22/46 (48 %)	8/22 (36 %) restarted ADA 18/22 (82 %) failed from LDA	Not specified	Not reported due to too small number of successful discontinuation ($n = 4$)
11	Kaine ALLOW USA [33]	Abatacept	MTX (≥10 mg/w)	6.6 y (mean)	Randomized	12 wks	80/120 (66 %) were randomized	79/80 were forced at 12 wks after randomization	30 % at restart to 63.5 % after 12 wks	Not described.
12	van der Maas Netherlands [28]	Infliximab	DMARDs	12 y (median)	DAS28 <3.2 for >6 mo	1 y (down-titrate 25 % of original dose/every 8–12 wks)	16 %	Not specified	Not specified	Not identified
13	Smolen PRESERVE International [12]	Etanercept	MTX 15–25 mg/wk	6.9 years (mean)	Sustained DAS28 - LDAS at wk 36 with MTX + ETN	52 wks (total 88 wks)	202 reduced ETN to 25 mg, 200 discontinued ETN	42/201 (20.9 %) in ETN 25 mg group, 116/200 (57.4 %) in ETN discontinued group failed from LDAS	Not specified	Not described
14	Detert HIT HARD Germany [25]	Adalimumab	MTX 15 mg sc	1.8 mo (median)	No criteria, All pts of 2 Randomized groups (PBO or ADA w/MTX) to continue MTX mono after wk 24	24 wks (total 48 wks)	87 discontinued ADA at week 24	11.5 % (5.5 %/47.9 %) failed from DAS28 <2.6 at 24 wks after ADA discontinuation	Not specified	Not described
15	Smolen OPTIMA Europe, USA [12]	Adalimumab	MTX	3.9 mo (mean)	DAS28 <3.2 at wks 22 and 26	52 wks after db period (wk 0–26), total 78 wks	44 % (207/466) in stable DAS28 < 3.2 discontinued ADA	35 % (26/75) failed from stable DAS28 <3.2 during wks 52–78	Not specified	Not described
16	Smolen CERTAIN Europe [13]	Certolizumab Pegol	Conventional DMARDs	4.5 y (mean), 3.5 y (median)	CDAI-LDA/MDA (6–16) at wk 20 and 24 in db period (CZP + DMARDs)	28 wks (wk 24–52, total 1 y)	18 discontinued CZP	14/18 (78 %) failed from CDAI-REM, 10/17 (59 %) failed from CDAI-LDA, 13/17 (76 %) failed from SDAI-REM, 13/17 (76 %) failed from DAS28-REM	Not specified	Not described

Table 1 continued

	Authorstudy nameCountry	Targeted discontinuing drug	Concomitant DMARDs	Symptom duration	Criteria for discontinuation	Follow up period	Number/of patients with discontinuation	Ratio of and time to restart/failed	Effect of restart	Predictors of successful discontinuation
17	Østergaard DOSERA Europe [11]	Etanercept	MTX	13.6 y (mean)	DAS28(ESR) <3.2 for 11 (retrospective) + 2 (ensure stable REM/ LDA) mo with ETN50 mg + MTX	48 wks	27 reduced ETN to 25 mg 23 discontinued ETN	15/27 (56 %) in ETN reduced group 20/23 (87 %) in ETN discontinued group; Failed (DAS28 >3.2 + ≥0.6 increase)	Not specified	Not described
18	Chatzidionysiou ADMIRE Sweden [9]	Adalimumab	MTX	8 y (median)	DAS28 <2.6 for >3 mo	28 wks (final 52 wks as whole period of protocol)	16/33 discontinued ADA, 15 evaluated at endpoint	12/15 (80 %) experienced at least 1 flare (DAS28 >2.6 or increase >1.2)	Not specified	Not described
19	Tanaka HONOR Japan [8]	Adalimumab	MTX	7.5 y (mean)	DAS28 <2.6 for ≥6 mo without NSAIDs or GCs	1 y	51/196 (26 %) discontinued ADA	64 % failed from DAS28 <2.6, 51 % filed from SDAI-REM, 9/50 (18 %) restarted ADA	90 % in DAS28 <32, 50 % in DAS28 <2.6 within 6 mo after restart	DAS28 ≤1.9 at discontinuation
20	Takeuchi ORION Japan [14]	Abatacept	Not specified	6.4 y (mean)	DAS28-CRP <2.3 at the end of a Japanese phase II/ III study of ABT	52 wks	34/51 (78 %) fulfilled the inclusion criteria	58.8 % failed from DAS28-CRP <2.3, 41.2 % failed from DAS28-CRP <2.7	Restart ABT if DAS28-CRP >2.7 at 2 consecutive visits, but the number or the ratio not described in the abstract	HAQ-DI ($p = 0.036$) and CRP level ($p = 0.048$) at the entry of ORION
21	Huizinga ACT-RAY Netherlands [15]	Tocilizumab	MTX or PBO	8.2 y (mean)	DAS28 <2.6 at 2 consecutive visits 12 wks apart in study year 2	up to 1 y (during study year 2)	213 discontinued TCZ	179/213 (84 %) experienced flare before year 2	Responded well to TCZ reintroduction (detailed number not described)	Not described
22	Wevers-De Boer IMPROVED Netherlands [34]	Adalimumab (after failing to achieve to DAS <1.6 by MTX25 mg + PSL 60 tapered to 7.5 mg in 7 wks	MTX	17 mo (median)	DAS <1.6 (stepwise tapering protocol, finally to drug free)	2 years	8 % (7/83) achieved drug-free remission, biologics free not specified	Not specified	Not specified	RF negativity (OR 95 % CI 0.6 (0.4–0.97, adjusted for baseline TJC)
23	Emery PRIZE Europe [26]	Etanercept 50 mg/wk	MTX 10–25 mg	6.5 mo (mean)	DAS28 <2.6	39 wks	63 discontinued ETN but continued MTX 65 discontinued both ETN and MTX	23/63 (36.5 %) in ETN-discontinued, 50/65 (76.9 %) in ETN + MTX-discontinued failed from DAS28-REM at 39 wks	Not specified (if DAS28 ≥32, GC boost at wks 56 or 64)	Not described

Table 1 continued

	Authorstudy nameCountry	Targeted discontinuing drug	Concomitant DMARDs	Symptom duration	Criteria for discontinuation	Follow up period	Number/of patients with discontinuation	Ratio of and time to restart/failed	Effect of restart	Predictors of successful discontinuation
24	Emery AVERT Europe [35]	Abatacept (randomized to sc ABT 125 mg + MTX ($n = 119$), ABT 125 mg monotherapy ($n = 116$) or MTX alone ($n = 116$))	MTX or monotherapy (randomized)	0.56 y (mean)	DAS28-CRP <3.2 at mo 12	Following 6 mo, (if DAS28-CRP <3.2 at mo 12, withdraw all drugs including ABT, MTX, other DMARDs, GCs)	All with DAS28-CRP < 3.2 discontinued both ABT and MTX	85.2 % in ABT + MTX group, 87.6 % in ABT mono group, 92.2 % in MTX mono group failed from DAS28-CRP <3.2 at 6 mo after stopping	Not specified	Not described
25	Nishimoto DREAM Japan [16]	Tocilizumab monotherapy (SAMURAI study)	None	7.8 y (median)	DAS28-ESR ≤3.2	52 weeks	187 discontinued TCZ	64.9 % (at 24wks), 86.6 % (52wks) failed from DAS28-ESR ≤3.2	139/157 (88.5 %) achieved DAS28-ESR <2.6 at 12 wks of TCZ retreatment	Low serum IL-6 (<12.9 pg/mL) and MMP-3 within normal range
26	Aguilar-Lozano Mexico [36]	Tocilizumab	MTX (no detailed explanation in abstract)	14 y (mean)	DAS28 ≤2.6	12 mo	45 discontinued TCZ	56 % relapsed	Not specified, (Retreatment using other agents achieved LDA or REM)	Not described in abstract
27	Pham STRASS France [29]	Etanercept or Adalimumab	Monotherapy or combination with MTX or LEF	9.5 y (mean)	ETN or ADA >1 y, and DAS28 <2.6 for >6 mo	18 mo	47/64 (73.4 %) in spacing injection arm tapered TNFi, at 18 mo	52/64 (81 %) relapsed	Not specified	Low DAS28 at baseline and a maintenance strategy

ABT abatacept, *ACR50* American College of Rheumatology 50 % improvement, *ACR75* 75 % improvement, *ADA* adalimumab, *BL* baseline, *CDAI* clinical disease activity index, *CZP* certolizumab pegol, *DAS28* disease activity score in 28 joints, *DAS28-CRP* DAS28 C-reactive protein, *DAS28-ESR DAS28* erythrocyte sedimentation rate, db double-blind, *DMARD* disease-modifying anti-rheumatic drug, *ETN* etanercept, *GC* glucocorticoid, *HAQ-DI* health assessment questionnaire disability index, *IFX* infliximab, *LEF* leflunomide, *LDA* low disease activity, *LDAS* low disease activity state, *MDA* moderate disease activity, *MMP-3* matrix metalloproteinase-3, *mo* month, *MTX* methotrexate, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PBO* placebo, *PSL* prednisone, *pts* patients, *REM* remission, *sc* subcutaneous, *SDAI* simplified disease activity index, *SJC* swollen joint count, *TCZ* tocilizumab, *TJC* tender joint count, *TNFi* TNF-inhibitor, *wk* week, *y* year

rates of LDA (91 %) measured by DAS28-ESR in the adalimumab continuation group were significantly higher than those (48 and 62 %, respectively) in the adalimumab discontinuation group 1 year after the continuation or discontinuation decision was made. Re-administration of adalimumab to patients with flare was effective in returning LDA within 6 months in 90 % and 9 months in 100 % patients. In the analysis of predictive factors related to sustaining remission for 1 year, only DAS28-ESR had a marked correlation with sustained remission in multivariate analyses. Subsequent ROC analysis for high estimation of sustained remission indicated a cut-off value for the adalimumab-free remission of 1.98. In patients with DAS28-ESR $\leq$1.98 at the discontinuation, their remission rates were approximately 70 % at 1 year after the discontinuation, indicating that "deep remission" would be a key for successful discontinuation of adalimumab in established patients with RA.

3.3 ADMIRE Study

In the ADMIRE study, 33 RA patients (median disease duration 8 years) in stable DAS28 remission for more than 3 months with MTX plus adalimumab were randomized to continue adalimumab or to discontinue it for 52 weeks [9]. At 28 weeks, 15 of 16 (94 %) and 5/15 (33 %) in an adalimumab-continued group and in the discontinued group, respectively, were in DAS28-remission. In long-term extension of the BRIGHT study, 46 RA patients (mean disease duration 10.3 years) whose DAS28-CRP was less than 2.7 by MTX plus adalimumab were randomized to a continued group or discontinued group. Only 4 of 22 adalimumab-discontinued patients (18.2 %) maintained LDA through week 52 [10].

3.4 DOSERA Study

In the DOSERA study, 73 RA patients (average of disease duration 13.6 years) in stable LDA for more than 11 months with MTX plus etanercept were randomized to MTX plus etanercept 50 mg/week, 25 mg/week or placebo. The percentage of non-failures at 48 weeks was 52 % for etanercept 50 mg, 44 % for etanercept 25 mg and 13 % for placebo groups [11]. In the PRESERVE study, after patients with moderately active RA despite MTX were treated with etanercept 50 mg/week and MTX for 26 weeks, 604 patients who achieved LDA were randomized to MTX plus etanercept 50 mg/week, 25 mg/week or placebo [12]. At weeks 52 after the randomization, sustained LDA was observed in 82.6 % of patients treated with MTX plus etanercept 50 mg/week, 79.1 % of those with MTX plus etanercept 25 mg/week and 42.6 % of those with MTX alone.

3.5 ORION Study

In the ORION study, abatacept was discontinued in 34 RA patients (mean disease duration 6.4 years) with a DAS28-CRP remission on MTX plus abatacept. At 52 weeks after the withdrawal, 58.8 % failed from DAS28-CRP remission [14].

3.6 ACT-RAY Study

In the ACT-RAY study, 556 established RA patients (mean disease duration 8.2 years) who inadequately responded to MTX were randomized to either add TCZ 8 mg/kg to MTX or to switch to TCZ 8 mg/kg with oral placebo [15]. About 50 % of patients entering into year 2 discontinued tocilizumab after achieving DAS28 $<$2.6 at 2 consecutive visits and 86 % of these patients experienced flare before the end of year 2. In the DREAM study, 187 established RA patients who showed LDA or remission by DAS28, median disease duration was 7.8 years, preceding tocilizumab monotherapy period was 4.0 years and DAS28 was 1.5, discontinued tocilizumab [16]. Only 13.4 % of them kept LDA, but 9.1 % fulfilled drug-free remission at 52 weeks.

There results indicate that patients with established RA in sustained remission or LDA after the discontinuation of a bDMARD were controversial among studies or difficult in many studies and the proportion of patients who could successfully discontinue bDMARDs ranged from 9 to 48 % at 1 year. However, from HONOR study and RRR study, deep remission is required to sustain remission after the discontinuation of a bDMARD and DAS28-ESR cut-off point at discontinuation was 1.98 achieving remission at week 52 in the adalimumab discontinued group and 2.22 for achieving LDA at week 52 in the infliximab-free group [6–8]. In fact in HONOR study, approximately 80 % patients with deep remission (DAS28-ESR $\leq$1.98) were able to sustain LDA for 1 year without adalimumab, whereas, only 42 % patients with mild remission were able to do so, although there was no statistically significant difference between the two groups. Meanwhile, 60 % patients with mild remission experienced flaring within a year, suggesting that mild remission may be insufficient for the discontinuation and that adalimumab should be continued in such patients even under DAS28 remission. Thus, "treatment holiday", successful discontinuation of a bDMARD for a certain period, is now feasible in some patients with long-standing RA encountered during routine clinical practice, but "deep remission" at the discontinuation is required to keep the treatment holiday of bDMARDs.

In our institution, among 619 patients including both early and established RA who were treated with infliximab

plus MTX, 102 patients reached bDMARD-free remission (manuscript in preparation). The baseline factors affecting infliximab-free remission were disease duration and rheumatoid factor (RF), indicating that patients with early RA have more chance to discontinue bDMARDs after obtaining remission.

4 Treatment Holiday from bDMARDs in Early RA

In early RA patients several studies including TNF20, OPTIMA, HIT HARD, IDEA, PRIZE, EMPIRE and BeSt have been undertaken to investigate whether remission can be sustained after a bDMARD targeting TNF is discontinued after following disease control.

4.1 TNF20 Study

The study regarding bDMARD-free treatment in RA patients was first reported by a TNF20 study [17, 18]. Patients with early RA who had less than 12 months of symptoms were treated with a combination of infliximab and MTX. One year after stopping induction therapy, response was sustained in 70 % of patients who received infliximab and MTX. A significant reduction in magnetic resonance imaging evidence of synovitis and erosions at 1 year was also observed.

4.2 BeSt Study

The Behandelstrategieën (BeSt) study was conducted to compare 4 treatment strategies and to observe clinical outcomes in patients with early RA (disease duration less than 2 years after onset, mean disease duration 0.8 years) [19–23]. In BeSt study 508 patients with high disease activity were distributed to 4 groups and were evaluated by DAS44 every three months. If DAS44 >2.4 (intermediate or high disease activity), change or addition of medications is required, if DAS44 $\leq$2.4 (remission or LDA), current medication is continued, and if DAS44 $\leq$2.4 continued over 6 months, decrease and/or discontinue concomitant medications including infliximab. In the fourth group who started by infliximab 90 patients of 120 (75 %) achieved LDA and infliximab was withdrawn in 77 cases because they maintained LDA for 6 months. The LDA was kept in 43/77 patients (56 %) for at least 1 year. Furthermore, more than half of patients who discontinued infliximab successfully maintained LDA for more than 8 years, according to the 8-year follow-up of infliximab-free survival in patients with early RA.

4.3 IDEA Study

In the IDEA study, patients with DMARD-naïve early RA were randomized to MTX plus infliximab and MTX plus intravenous steroid therapy as remission induction [24]. In the former group, 24.5 % (14/55) had stopped infliximab due to sustained remission (DAS44 <1.6 for 6 months) and 78.6 % (11/14) of them maintained remission for half a year.

4.4 OPTIMA Study

A multinational, double-blinded, randomized controlled study was performed to determine the optimal protocol for treatment initiation with adalimumab plus MTX in patients with RA (OPTIMA) [12]. In this study, the withdrawal of adalimumab in early RA patients (with a mean RA duration of 3.9 months) was also assessed. Outcomes of withdrawal or continuation of adalimumab were assessed in patients who achieved a stable LDA target after 26 weeks of initially assigned treatment with adalimumab and MTX. Of the 466 RA patients treated with adalimumab and MTX, 207 (44 %) achieved the stable LDA measured by DAS28-CRP at weeks 22 and 26 and were re-randomized to placebo plus MTX or adalimumab plus MTX during the second study period for 52 weeks. After 52 weeks, 91 and 86 % of patients who continued adalimumab treatment maintained LDA and remission, respectively, compared with 81 and 66 % of patients who withdrew from adalimumab treatment.

4.5 HIT HARD Study

In a HIT HARD study, the withdrawal of adalimumab in patients with early RA (mean RA duration 1.7 months) was also assessed whether an early induction therapy with subsequent step down strategy leads to a long-term clinical effect in early RA patients as compared to initial and continued MTX [25]. During the first 24 weeks, 172 patients were treated with adalimumab or placebo with MTX; after week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase, 47 % of patients treated with MTX and adalimumab achieved DAS28-remission; at week 48, 44 % of these patients were still in remission by 24 weeks of adalimumab-free treatment.

4.6 PRIZE Study

In the PRIZE study MTX-naïve early RA patients with moderately active disease activity were treated with etanercept and MTX and DAS28 remission was achieved by 70 % of patients [26]. These patients were randomized to a

double-blinded 39-week period of reduced-dose etanercept (25 mg) plus MTX, MTX plus subcutaneous placebo, or oral placebo and subcutaneous placebo. At week 39 the sustained remission was observed in 63.5 % of patients with etanercept plus MTX, 38.5 % with MTX, those who discontinued etanercept, and 23.1 % with placebo, those who discontinued etanercept and MTX. There was no significant radiographic progression in any treatment group.

4.7 EMPIRE Study

In EMPIRE study, 110 DMARD-naïve patients with early inflammatory arthritis and the minimum of one synovitis joint were randomized to MTX plus etanercept or MTX plus placebo for 52 weeks [27]. Injections were stopped in all patients at week 52 or injections were stopped early in those with no tender or swollen joints for more than 26 weeks. In the MTX + ETN group, 41.9 and 57.7 % remained in remission and LDA according to DAS28, respectively, from week 52 to week 78.

Taken together, these recent studies indicate that 30–79 % of early RA patients could discontinue bDMARDs without clinical flare and functional impairment after reduction of disease activity to LDA or remission by bDMARDs in combination with MTX. Although there are limited studies, a treatment holiday of bDMARDs is now feasible in approximately half of patients with early RA.

5 De-Escalation of bDMARDs in RA

On the other hand, de-escalation (dose reduction/interval prolongation) of bDMARDs appears to attract attention because complete discontinuation of bDMARDs is rather difficult for the established RA patients. A group in the Netherland performed the first observational cohort study regarding de-escalation of bDMARDs in RA patients with stable LDA and reported that the down-titration of infliximab was feasible for 45 % of patients, with a mean dose reduction of 60 % after 1 year [28]. In the PRESERVE study, patients with RA achieving remission after 1-year treatment with etanercept were randomly assigned with full-dose maintenance (50 mg weekly), dose reduction (25 mg weekly) or discontinuation for 1 year [12]. However, dose reduction was associated with a non-significant risk of relapse and structural damage progression at 1 year as compared to full-dose maintenance. Recent interval prolongation STRASS study, an 18-month randomized controlled trial, was undertaken by a French group to compare the impact of a DAS28-driven step-down strategy to maintenance strategy [29]. Established RA patients, with etanercept or adalimumab for longer than 1 year, DAS28 remission for more than 6 months, stable damage on X-rays, were randomized to TNF-inhibitor injection spacing arm ($n = 64$) and a maintenance strategy arm ($n = 73$), then followed every 3 months for 18 months. The inter-injection interval was increased every 3 months up to full stop at 4th step. At 18 months, 47 (73.4 %) patients of the spacing arm tapered TNF-blockers. Mean DAS28, mean HAQ and structural damage progression were not significantly different between arms. However, relapse (ΔDAS28 > 0.6 + DAS28 > 2.6) occurred at least once more frequently in the spacing arm than in the maintenance arm (81 vs. 56 %, $p = 0.0009$).

However, in these studies it is not clear how to monitor the disease activity and retreat or increase the dose in case of disease worsening after dose reduction, which may rather result in equally good care as just continuing treatment. Furthermore, when considering de-escalation trials, there are quite various factors underlying to de-escalate bDMARDs. For instance, (i) baseline characteristics; early or established RA, with or without MTX and/or other DMARDs, LDA or remission, remission criteria, duration of disease control and so on, (ii) targeted medications; bDMARDs or MTX, TNF-inhibitors or non-TNF-bDMARD, dose reduction or interval prolongation, schedule of the dose reduction, criteria for de-escalation, reduction of all at once and many, (iii) disease flare after de-escalation; definition of flare, how to treat flared cases, restart all or step-up at flare and etc. Thus, there are too many factors regarding the de-escalation, very careful consideration regarding inclusion criteria, protocol, assessment, etc. would be required to perform de-escalation trials in RA patients. On the other hand, although titrating patients to the lowest dose may save medication costs, it may also lead to increased number of patient contacts and consequent costs. So far, none of the previous controlled de-escalation studies included a disease activity guided strategy or cost-effectiveness analyses. Taken together, in this manuscript we have shed light upon discontinuation of bDMARD rather than de-escalation strategy.

6 Conclusion

The combination of MTX and bDMARDs targeting TNF, IL-6 and T cells has revolutionized RA treatment, leading to clinical, functional and structural remission. Since we have obtained strong weapons to treat RA, a new strategy rather than a new target should be required for the advanced therapy of RA. For instance, how and when bDMARDs are discontinued without disease flare is an emerging theme to strategically treat RA. We are now in a position to evaluate what is possible in terms of maintaining remission or LDA while at the same time reducing

the burden of treatment on the patient and healthcare system. Data emerging from large, well-conducted studies indicate that approximately half of early RA patients could discontinue bDMARDs targeting TNF without clinical flare and functional impairment after obtaining reduction of disease activity to LDA or remission by bDMARDs in combination with MTX. Saleem et al. [30] also reported that a TNF-inhibitor-free sustained remission rate was 60 % after acquiring DAS28 remission in MTX-naïve early RA patients. Within the initial treatment group, the only clinical predictor of the successful discontinuation was shorter symptom duration prior to receiving therapy (median 5.5 vs. 9.0 months, $p = 0.008$). No other clinical features including activity measured by power doppler were associated with the discontinuation of bDMARD.

However, fewer patients sustained remission or LDA after the discontinuation of bDMARDs for patients with established RA, compared to early RA. It is often difficult to successfully discontinue bDMARDs and the results were controversial among studies. The HONOR study and RRR study indicated that "deep remission" is required to successfully discontinue bDMARDs in established RA patients; DAS28-ESR cut-off point at discontinuation was 1.98 achieving remission at week 52 in the adalimumab withdrawal group and 2.22 for achieving LDA at week 52 in the infliximab-free group [6–8]. Thus, the mild remission is insufficient for the discontinuation and bDMARDs should be continued in such patients even under DAS28 remission.

Thus, "treatment holiday" of bDMARDs is now feasible in some patients with RA with long-standing RA, but "deep remission" at the discontinuation is a key factor to keep the treatment holiday of bDMARDs. However, such intensive treatment would have the potential of reducing drug-induced adverse effects and reducing long-terms medical costs, although the risks of worsening clinical, structural and functional outcomes should be considered with careful monitoring.

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