CHAPTER 9

Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission

Exploratory analyses from the BeSt study

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ABSTRACT

Objectives: To determine the relapse rate after discontinuing treatment in patients with rheumatoid arthritis (RA) in sustained clinical remission, to identify predictors of a relapse and to evaluate treatment response after restarting treatment.
Methods: Five-year data from the BeSt study were used, in which 508 patients with recent-onset RA were randomised into four dynamic treatment strategies, aiming at a disease activity score (DAS) ≤2.4. When DAS was <1.6 for ≥6 months the last disease-modifying antirheumatic drug (DMARD) was tapered and discontinued. If DAS increased to ≥1.6, the last DMARD was immediately reintroduced.
Results: During a 5-year period, 115/508 patients (23%) achieved drug-free remission. Of these, 53 patients (46%) restarted treatment because DAS was ≥1.6 after a median of 5 months, 59 patients (51%) remained in drug-free remission for a median duration of 23 months, and 3 (3%) were lost to follow-up. In those who restarted treatment, mean (SD) DAS increased from 1.13 (0.73) at remission before tapering to 2.18 (0.65) at restart, reflecting an increase in all four components of DAS. Multivariable predictors for restarting treatment were anti-cyclic citrullinated peptide (anti-CCP), last DMARD sulphasalazine, low baseline health assessment questionnaire score and high mean DAS until remission. Of the 53 patients who restarted treatment, 39 (74%) again achieved remission 3-6 months after the restart. The median (IQR) damage progression in those who restarted treatment during the year of DAS increase was 0 (0-1) Sharp-van der Heijde units.
Conclusion: During 5 years DAS-steered treatment, nearly 25% of patients with RA achieved drug-free remission; 46% restarted DMARD monotherapy because of a relapse, the large majority of whom again achieved clinical remission within 3-6 months without showing radiological progression during the relapse.

INTRODUCTION

As a result of the increasing percentage of patients achieving remission with the introduction of early, intensive goal-steered therapy,[1] more often the dilemma is whether a patient with rheumatoid arthritis (RA) in prolonged remission could discontinue disease-modifying antirheumatic drugs (DMARDs) or whether treatment should be continued. Stopping DMARDs while keeping remission would be beneficial with respect to adverse events and costs. On the other hand, discontinuation of DMARDs could contribute to a relapse of disease with potential harmful consequences.
Historically, the question whether DMARD therapy can be discontinued has often been asked. Several small studies from the 1970s/1980s assessed the need for long-term DMARD maintenance therapy in patients treated according to the pyramid 'go low go slow' approach.[2-8] These studies reported high relapse rates after discontinuation of DMARDs (range 58%-100%). Later, ten Wolde, et al. performed a randomised clinical trial in 285 patients with long-standing inactive RA [9,10] and reported flare rates of 38% in the placebo (discontinuation) group versus 22% in the group continuing DMARD therapy. Data on withdrawal of DMARDs in patients with established disease have recently been summarised in a meta-analysis.[11]
Since the approach of RA treatment has shifted towards early intensive goal-steered treatment, the discontinuation of DMARDs has rarely been studied.[12,13] There are few data on the safety of withdrawing DMARDs, the chance of flares and the response to reintroduction of DMARDs.[10] In addition, it is unclear whether a flare after a drug-free remission episode can be predicted. With prediction subgroups of patients might be identified in which medication can be safely withdrawn versus other subgroups in whom treatment should be continued.
The protocol of the BeSt study, a randomised clinical trial in recent-onset RA, allowed discontinuation of DMARDs in patients in prolonged remission under strict control of disease activity.[14] The objectives of this analysis were: (1) to assess the flare rate in patients in drug-free remission; (2) to describe the severity of relapse; (3) to identify predictors for relapse; and (4) to assess the response to reintroduction of DMARDs.

METHODS

Study design and patients

Five-year data of the BeSt study were used. Details of the design have been described elsewhere.[15] In summary, 508 patients with recent-onset active RA according to the 1987 RA classification criteria (disease duration <2 years)[16] were randomised into four treatment strategies: sequential monotherapy (n=126), step-up combination therapy (n=121), initial combination therapy with prednisone (n=133), and initial combination therapy with methotrexate and the tumour necrosis factor α inhibitor infliximab (MTX+IFX, n=128). Treatment was adjusted based on 3-monthly disease activity score (DAS) measurements (Disease Activity Score 44 joints, DAS44), aiming at DAS ≤2.4.[17,18] If DAS was >2.4 the next

step of the protocol was taken. If DAS was ≤2.4 for ≥6 months, treatment was tapered to the maintenance dose. For details on treatment steps per arm see *figure 1* in *chapter 4*.

Discontinuation of DMARD therapy

Remission was defined as a DAS <1.6.[19] Two years after inclusion, the protocol allowed tapering and discontinuation of the last DMARD if patients fulfilled the following conditions: (1) DMARDs in maintenance dose according to the protocol (2) clinical remission (defined as DAS <1.6) for ≥6 months.

For MTX monotherapy, sulphasalazine (SSA) monotherapy, leflunomide and intramuscular gold, the maintenance doses were 10 mg/week, 2000 mg/day, 10 mg every other day and 50 mg every other week, respectively. All combinations were first tapered to MTX monotherapy which was then tapered to 10 mg/week, with the exception of the COBRA combination (MTX, SSA, prednisone)[20] which was tapered to SSA 2000 mg/day as maintenance dose, and the combination azathioprine and prednisolone which was tapered to azathioprine 2 mg/kg/day.

Discontinuation of the last DMARD occurred by tapering MTX with 2.5 mg/4 weeks and SSA with 500 mg/4 weeks; maintenance doses leflunomide, gold and azathioprine were simply discontinued.

Restart of DMARD therapy

If the DAS was ≥1.6, the last tapered DMARD was immediately restarted in maintenance dose and could not be discontinued twice. Patients who remained drug-free until year 5 will be referred to as 'sustained drug-free remission patients (SDFR)' whereas patients who restarted before 5 years will be called 'restarters'.

Statistical analysis

The software program SPSS version 17.0 was used for all statistical analyses. Among the patients who achieved drug-free remission, variables associated with restarting treatment were identified by univariable logistic regression using characteristics from baseline and from the last visit before tapering the last DMARD to 0. A multivariable logistic regression with univariable logistic determinants ($p<0.10$) was used to identify independent predictors for restart using a backward selection procedure ($p<0.05$). Subsequently, the multivariable predictors from the backward procedure were entered in a new logistic regression model. Variables that were not associated with restarting treatment in the univariable logistic regression were then added one by one to assess whether they had additional predictive value.

RESULTS

After 5 years 115/508 (23%) patients achieved drug-free remission with no significant differences between the groups (p=0.20, *table 1*). Of these, 53 (46%) restarted treatment after a median (IQR) period of 5 (2–16) months. Fifty-nine (51%) remained in drug-free

TABLE 1 Overview of the distribution of patients who achieved drug-free remission during 5 years of follow-up in the four treatment groups.

	Sequential monotherapy (n=126)	Step-up therapy (n=121)	Initial combo with prednisone (n=133)	Initial combo with infliximab (n=128)
Drug-free ever	31	24	24	36
Still drug-free at t=5 year	14 (45)	14 (58)	10 (42)	21 (58)
Restarted DMARD monotherapy	15 (48)	9 (38)	14 (58)	15 (42)
Lost to follow-up	2 (6)	1 (4)	0 (0)	0 (0)

Data are presented as n (%).
DMARD, disease-modifying antirheumatic drug.

TABLE 2 Treatment details of the 115 patients who discontinued all DMARDs due to sustained clinical remission

		Sustained drug-free remission (n=59)	Restarted (n=53)	Lost to follow-up (n=3)
Sequential monotherapy	MTX mono[1]	11	9	1
	SSA mono[2]	0	4	1
	Leflunomide mono[3]	3	0	0
	MTX + IFX[4]	0	2	0
	Next steps	0	0	0
Step-up combination therapy	MTX mono[1]	8	4	1
	MTX + SSA[5]	4	3	0
	MTX + SSA + HCQ[5]	2	1	0
	MTX + SSA + HCQ + pred[5]	0	1	0
	Next steps	0	0	0
Initial combination with prednisone	MTX + SSA + pred[6]	10	12†	0
	MTX + CSA + pred[7]	0	2	0
	Next steps	0	0	0
Initial combination with infliximab	MTX + IFX[4]	19	13	0
	SSA mono[2]	2	2	0
	Next steps	0	0	0

For each treatment group, the medication step at which the drug-free remission was reached is shown separately for the sustained drug-free remission patients, restarters and patients lost to follow up. Before the protocol allowed discontinuation of the last DMARD, patients had to taper their medication to DMARD monotherapy in a maintenance dose. If subsequently DAS fell to <1.6 for ≥6 months, the last DMARD could be tapered/discontinued. Details on tapering and discontinuation are shown below.

1 First MTX was tapered to 10 mg/week if DAS ≤2.4 during ≥6 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during ≥6 months on MTX 10 mg/week.
2 SSA was tapered to 0 if DAS <1.6 during ≥6 months on SSA 2000 mg/day.
3 First leflunomide was tapered to 10 mg every other day if DAS ≤2.4 during ≥6 months. Subsequently, leflunomide was discontinued if DAS <1.6 during ≥6 months on leflunomide 10 mg every other day.
4 First IFX was discontinued and MTX was tapered to 10 mg/week if DAS ≤2.4 during ≥6 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during ≥6 months on MTX 10 mg/week.
5 First, the step-up combination was tapered to MTX monotherapy, and then to MTX 10 mg/week if DAS ≤2.4 during ≥6 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during ≥6 months on MTX 10 mg/week.
6 First prednisolone and MTX were tapered to 0 if DAS ≤2.4 during ≥6 months. Subsequently, SSA was tapered to 0 if DAS <1.6 during ≥6 months on SSA 2000 mg/day.
7 First prednisolone and CSA were tapered to 0 if DAS ≤2.4 during ≥6 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during ≥6 months on MTX 10 mg/week.
† One patient tapered to MTX 10 mg/week due to SSA toxicity.
CSA, ciclosporin A; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; IFX, infliximab; MTX, monotherapy; pred, prednisolone; SSA, sulphasalazine.

TABLE 3 Univarable analysis: potential variables associated with a flare during a drug-free remission period

	Restarters (n=53)	Sustained drug-free remission (n=59)	OR (95% CI)
I Baseline characteristics			
Age, mean (SD)	57 (13)	55 (15)	1.01 (0.99 – 1.04)
Female gender, n (%)	29 (55)	33 (56)	0.95 (0.45 – 2.01)
Symptom duration (wks), median (IQR)	24 (13 – 56)	20 (11 – 40)	1.00 (0.99 – 1.02)
DAS44, mean (SD)	4.2 (0.8)	4.3 (0.9)	0.82 (0.53 – 1.24)
HAQ, median (IQR)*	1.13 (0.56 – 1.38)	1.25 (0.75 – 1.88)	0.53 (0.29 – 0.97)*
SJC44, median (IQR)	13 (10 – 18)	15 (10 – 21)	0.97 (0.92 – 1.03)
RAI, median (IQR)	11 (8 – 14)	11 (7 – 16)	0.97 (0.92 – 1.03)
VAS global health, mean (SD)*	47 (31 – 61)	53 (41 – 70)	0.98 (0.96 – 1.00)*
ESR, median (IQR)	36 (18 – 51)	31 (15 – 45)	1.01 (0.99 – 1.02)
CRP, median (IQR)	18 (9 – 38)	20 (6 – 45)	1.00 (0.99 – 1.01)
SHS, median (IQR)	2.5 (1.0-7.0)	1.5 (0 – 6.0)	1.03 (0.98 – 1.09)
Erosive yes, %	24 (43)	32 (60)	2.0 (0.95 – 4.4)
Anti-CCP positive, %*	37 (70)	18 (31)	5.3 (2.4 – 11.8)*
RF positive, %*	37 (70)	26 (44)	2.9 (1.3 – 6.4)*
Sequential monotherapy (group 1)	15 (28)	14 (24)	Reference
Step-up combination therapy (group 2)	9 (17)	14 (24)	0.60 (0.20 – 1.8)
Initial combination with prednisone (group 3)	14 (26)	10 (17)	1.3 (0.44 – 3.9)
Initial combination with infliximab (group 4)	15 (28)	21 (36)	0.67 (0.25 – 1.79)
II Characteristics at visit before discontinuation			
DAS44, mean (SD)	1.1 (0.4)	0.9 (0.5)	1.55 (0.67 – 3.58)
HAQ, median (IQR)	0.00 (0.00 – 0.25)	0.00 (0.00 – 0.13)	1.61 (0.50 – 5.20)
SJC, median (IQR)	0 (0 – 0)	0 (0 – 0)	1.18 (0.80 – 1.74)
TJC, median (IQR)	0 (0 – 1)	0 (0 – 0)	1.01 (0.73 – 1.40)
VAS global health, mean (SD)	15 (2 – 22)	10 (2 – 20)	1.01 (0.98 – 1.04)
ESR, median (IQR)	7 (5 – 15)	6 (4 – 15)	0.99 (0.96 – 1.03)
CRP, median (IQR)	5 (2 - 10)	3 (2 – 7)	1.02 (0.95 – 1.10)
SHS, median (IQR)	5.0 (1.5 – 9.5)	1.5 (0 – 7.8)	1.04 (0.99 – 1.10)
Last DMARD: MTX, n (%)	35 (66)	44 (75)	Reference
SSA, n (%)	17 (32)	12 (20)	1.8 (0.75 – 4.2)
other, n (%)	1 (2)	3 (5)	NA
DAS44, weighted mean until remission (SD)	1.6 (0.5)	1.5 (0.5)	1.6 (0.7 – 3.7)
HAQ, weighted mean until remission (SD)	0.35 (0.34)	0.29 (0.27)	2.0 (0.5 – 6.9)

In the upper part of the table baseline variables are shown and, in the bottom part of the table, characteristics at the visit before the last DMARD has been tapered are given. The weighted mean DAS44 and HAQ until remission represents the mean DAS44 and HAQ from baseline until the visit when the last DMARD is discontinued.
*p<0.05 without correction for multiple testing.
anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS44, disease activity score (44 joints); DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, interquartile range; MTX, methotrexate; n, number of patients; NA, not applicable due to low patient numbers; RAI, Ritchie articular index; RF, rheumatoid factor; SHS, Sharp-van der Heijde score; SJC44, swollen joint count 44 joints; SSA, sulphasalazine; VAS, visual analogue scale (mm).

remission with a median (IQR) duration of 23 (15–25 months) at 5 years, and 3 (3%) were lost to follow-up. Details of the treatment steps at which drug-free remission was reached are given in *table 2*.

In the restarters, mean (SD) DAS increased from 1.13 (0.73) at remission before tapering to 2.18 (0.65) at restart, reflecting an increase in all four components of DAS: median (IQR) erythrocyte sedimentation rate (ESR) increased from 7 (5–14) to 19 (7–28), swollen joint count from 0 (0–0) to 2.5 (0–4), Ritchie Articular Index[21] from 0 (0–1) to 3 (1–6), and visual analogue scale (VAS) global health from 15 (2–22) to 28 (15–55). In 38/53 of patients (72%) the highest disease activity during the flare was ≤2.4 (low disease activity), in 12/53 (23%) between 2.4-3.7 (moderate disease activity) and in 3/53 (6%) it was >3.7 (high disease activity).

The presence of anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor, lower VAS global health and lower health assessment questionnaire (HAQ) at baseline were univariably associated with restarting treatment *(table 3)*. Furthermore, baseline Sharp-van der Heijde (SHS) tended to be higher in those who restarted treatment than in SDFR patients (ns). None of the characteristics at the time of remission were associated with restarting treatment. In the multivariable analysis, the presence of anti-CCP was the strongest independent predictor for restart, followed by a higher mean DAS until remission, lower baseline HAQ and SSA as last DMARD *(table 4)*. Both restarters and SDFR patients had good functional ability during their remission *(table 3)*, comparable to HAQ scores of the general population (age- and sex matched: median [IQR] HAQ 0.20 [0.15– 0.34] and 0.18 [0.10–0.49] for restarters versus SDFR, respectively)[22]

Of the 53 restarters, 25 (47%) again achieved clinical remission within 3 months after restarting treatment with the last used DMARD in maintenance dose and another 14 (26%) within 6 months. Eleven patients (21%) achieved a DAS ≤2.4, one patient (2%) did not achieve a DAS ≤2.4 and two patients (4%) were lost to follow-up. The large majority of patients did not show joint damage progression in the first year after discontinuation of DMARDs, with a median (IQR) SHS progression of 0 (0–1) units in the restarters during the year of DAS increase compared with 0 (0–0) in the SDFR patients in the first year completely drug-free (p=0.44, Mann-Whitney-U test, *figure 1*).

TABLE 4 Multivariable predictors for a flare during a drug-free remission period

	OR	95% CI
Anti-CCP positive	7.5	2.9 – 19.4
Weighted mean DAS44 until remission	4.7	1.5 – 15.2
Baseline HAQ	0.41	0.19 – 0.88
Last DMARD: MTX	Reference	Reference
SSA	3.5	1.5 – 15.2
other	NA	NA

anti-CCP, anti-cyclic citrullinated peptide; DAS44, disease activity score (44 joints); DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; MTX, methotrexate; NA, not applicable due to low patient numbers; SSA, sulphasalazine

DISCUSSION

We implemented discontinuation of DMARDs early in the course of the disease in patients with RA in clinical remission, treated according to an early, aggressive and dynamic treatment approach. Twenty-three percent of patients could discontinue their DMARDs because of remission during ≥6 months: 51% of them remained in drug-free remission (median 23 months) and 46% restarted treatment. The majority of these restarters again achieved clinical remission within 3-6 months after restarting DMARDs without suffering joint damage progression.

Earlier reported relapse rates were comparable or higher (38-100%) [2-9,11,13] than the 46% relapse rate in our study. The largest well-designed study by ten Wolde, et al [9] in patients with established RA showed a relapse rate in the same range as the rate we found in our early RA cohort (38% versus 46%). Direct comparison of these relapse rates is difficult owing to different definitions of relapse/remission and differences in patient populations. In the older studies,[2-8,11] the majority of patients had long standing disease with significant joint damage and poor functional ability. We report discontinuation of DMARDs early in the disease course with the key advantage that patients in drug-free remission had limited joint damage and enjoyed a functional ability comparable to an age- and sex-matched healthy reference population.[22]

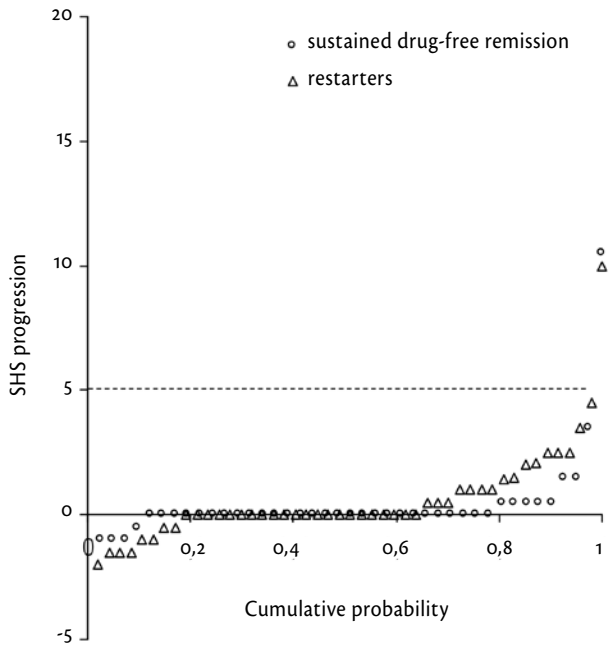

FIGURE 1 Cumulative probability plot showing radiological joint damage progression in the first year after stopping the last disease-modifying antirheumatic drug in patients who remained in clinical remission (circles) versus patients who restarted treatment (triangles). The dashed line represents a clinical relevant progression. SHS, Sharp-van der Heijde score.

Tanaka, et al recently published the RRR study on discontinuation of infliximab in patients with RA after attaining low disease activity.[23] As in our study, medication was withdrawn and reintroduced at a predefined cut-off and the occurrence of a flare was registered. This study differs from the BeSt study in several ways. First, in the RRR study, infliximab was discontinued while methotrexate was continued whereas, in the BeSt study, all antirheumatic treatment was withdrawn. Second, in the RRR study, infliximab was discontinued and reintroduced at the low disease activity cut-off point. No clinical remission was required. Furthermore, the disease duration at inclusion was higher in the RRR study (5.9 versus 0.4 years). Despite these differences in study design, the observed chance of a flare was remarkably comparable (45% versus 46%) and, as we found, the majority of patients responded well to reintroduction of treatment after a relapse.

The presence of CCP2 antibodies is one of the strongest known predictors for a worse disease course in RA.[24] In line with this, anti-CCP positive patients have a lower chance of achieving drug-free remission.[14] In addition, we found that among the patients achieving drug-free remission, the presence of anti-CCP was the strongest predictor for the occurrence of a flare. Nevertheless, 30% of the patients in sustained drug-free remission are anti-CCP positive, indicating that, even in anti-CCP positive patients, successful drug-free remission is possible.

Surprisingly, low HAQ at baseline was predictive for restarting treatment in the univariable and the multivariable analysis. The univariable results of VAS general health pointed in the same direction. This suggests that if patients are able to improve more in HAQ – that is, if patients have gained more (mean HAQ improvement 1.14 vs 0.83 in SDFR vs restarters) - they have a higher chance of retaining remission after discontinuation of drugs.

Patients who discontinued MTX maintenance therapy had a higher chance of retaining remission than patients who discontinued SSA. Although the patient numbers are low, these results may suggest that SSA is less potent in inducing sustained remission after discontinuation than MTX. Additional research is needed to confirm this finding.

We hypothesised that patients with a DAS just below the cut-off score of 1.6 might have a higher chance of relapse than patients with a lower DAS. We therefore assessed whether the level of inflammation at the time of remission, as measured with the DAS and its components was predictive for a flare. There appeared to be no association between inflammation measures and the risk of flare, indicating that the 'depth' of the DAS remission is not useful in predicting whether the remission will be maintained after discontinuation of DMARDs. 'Deeper' remission is not 'truer' remission in that sense.

During the relapse the duration and severity of a higher level of disease activity seems limited. DMARDs in a low maintenance dose were restarted immediately if DAS rose to ≥1.6 and the large majority again achieved clinical remission within 3-6 months. During the flare the DAS increased to a low disease activity level in 72% of patients; few experienced high disease activity during the flare. The temporarily higher DAS level might have contributed to the slightly higher (non-significant) joint damage progression in the restarters than in the SDFR patients. Another explanation could be that the restarters had less favourable characteristics than the SDFR patients, including a higher per-

centage of anti-CCP positive patients, leading to a higher risk of progression.[24] This is supported by the observation that, before discontinuing DMARDs, restarters already had more joint damage than patients retaining remission (median SHS 5.0 vs 1.5).

Since DMARDs were stopped in all patients in prolonged remission, it is unknown what the flare rate would have been if treatment had been continued. Ten Wolde, et al found that, in patients who continued therapy, the flare rate was also considerable (22%) but significantly lower than in patients discontinuing treatment (38%).[9] Being aware of the differences in patient population, these findings suggest that part of the flares we observed could have happened even if DMARDs were continued.

In summary, in 23% of patients with recent-onset RA, DMARDs could be discontinued because of prolonged clinical remission. Based on strict criteria, almost half of them had to restart treatment. The presence of anti-CCP was the strongest predictor for restarting treatment. The large majority of patients who lost remission remained in low disease activity, regained clinical remission shortly after reintroduction of low-dose mono-therapy and showed no joint damage progression in the year of the restart. We therefore propose that, under continued tight control, discontinuation of the last DMARD can be considered in patients in stable clinical remission. The final decision whether or not to withdraw treatment in an individual patient should be made by the physician and patient together, carefully weighing the advantages and disadvantages.

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