Cost-effective Tapering Algorithm in Patients with Rheumatoid Arthritis: Combination of Multibiomarker Disease Activity Score and Autoantibody Status

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ABSTRACT. ***Objective.*** To analyze the effect of a risk-stratified disease-modifying antirheumatic drug (DMARD)–tapering algorithm based on multibiomarker disease activity (MBDA) score and anticitrullinated protein antibodies (ACPA) on direct treatment costs for patients with rheumatoid arthritis (RA) in sustained remission.

Methods. The study was a posthoc retrospective analysis of direct treatment costs for 146 patients with RA in sustained remission tapering and stopping DMARD treatment, in the prospective randomized RETRO study. MBDA scores and ACPA status were determined in baseline samples of patients continuing DMARD (arm 1), tapering their dose by 50% (arm 2), or stopping after tapering (arm 3). Patients were followed over 1 year, and direct treatment costs were evaluated every 3 months. MBDA and ACPA status were used as predictors creating a risk-stratified tapering algorithm based on relapse rates.

Results. RA patients with a low MBDA score (< 30 units) and negative ACPA showed the lowest relapse risk (19%), while double-positive patients showed high relapse risk (61%). In ACPA-negative and MBDA-negative (< 30 units), and ACPA or MBDA single-positive (> 30 units) groups, DMARD tapering appears feasible. Considering only patients without flare, direct costs for synthetic and biologic DMARD in the ACPA/MBDA-negative and single positive groups (n = 41) would have been €372,245.16 for full-dose treatment over 1 year. Tapering and stopping DMARD in this low-risk relapse group allowed a reduction of €219,712.03 of DMARD costs. Average reduction of DMARD costs per patient was €5358.83.

Conclusion. Combining MBDA score and ACPA status at baseline may allow risk stratification for successful DMARD tapering and cost-effective use of biologic DMARD in patients in deep remission as defined by the 28-joint count Disease Activity Score using erythrocyte sedimentation rate. (J Rheumatol First Release December 1 2018; doi:10.3899/jrheum.180028)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DRUG COSTS MULTIBIOMARKER DISEASE ACTIVITY
TAPERING REMISSION ANTICYCLIC CITRULLINATED PROTEIN ANTIBODIES

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Rheumatoid arthritis (RA) is a prototype inflammatory disease with a prevalence of up to 1% worldwide. RA is characterized by chronic joint inflammation requiring longterm treatment[1]. Disease-modifying antirheumatic drug (DMARD) treatment of RA, though often highly effective, is associated with substantial healthcare costs and possible side effects related to longterm treatment. With the continuous improvement of RA therapy and treat-to-target strategies, the number of patients achieving a symptom-free state (remission) is steadily increasing, suggesting the need for stratified approaches for tapering and stopping DMARD treatment in patients with low risk of relapse[2,3].

The concept of tapering and stopping DMARD in RA patients in sustained remission has been discussed in a substantial number of clinical studies[4]. They indicated that in cases of stable clinical remission for more than 6 months, tapering and stopping of DMARD is feasible only in a subset of patients with RA. Quality of remission [e.g., deep remission such as Boolean, vs more "shallow" remission such as in the 28-joint count Disease Activity Score using erythrocyte sedimentation rate (DAS28-ESR)] may play a role in deciding whether a patient with RA experiences relapse. The key question is to define those patients in remission who can successfully taper and stop DMARD treatment. Such predictive modeling of successful versus unsuccessful DMARD tapering in remission would likely allow the prevention of overtreatment of RA patients, with the consequences of reducing side effects and drug costs[5].

In previous data from the RETRO study, a randomized prospective strategy study of DMARD tapering in RA patients in stable DAS28-ESR remission (< 2.6), we were able to show that the presence of autoimmunity [anticitrullinated protein antibody (ACPA) positivity] as well as elevation of serum biomarkers of inflammation [multibiomarker disease activity (MBDA)] were independent predictors for relapse, if DMARD were tapered and stopped[6,7]. The combination of ACPA status and MBDA has shown to be a possible feasible approach for defining prediction models of relapse risk in patients with RA in remission who are undergoing DMARD tapering[7].

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The aim of the present posthoc retrospective analysis of the prospective RETRO study was to show that tapering and stopping DMARD in RA patients in sustained clinical remission is feasible and cost-effective, especially in patients with low risk of relapse based on ACPA negativity and low MBDA status.

MATERIALS AND METHODS

Patients and inclusion criteria. RETRO is a phase III, prospective, multicenter, open, randomized, controlled, parallel-group study (EudraCT number 2009-015740-42; Figure 1)[6]. The primary objective of the RETRO trial was to evaluate the risk of having a relapse of RA despite tapering or stopping treatment in RA patients in sustained remission. Patients included had to fulfill the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria for RA[8]. Prior to study inclusion, patients had to be diagnosed with RA for at least 12 months. Further, patients had to be in stable clinical remission (DAS28-ESR < 2.6)[9] and taking stable doses of conventional (cDMARD) and biological DMARD (bDMARD) for at least 6 months. The present study was approved by the ethics committee of the Friedrich-Alexander-University of Erlangen-Nuremberg, Germany (approval number Az:01_2010) and all local ethics committees of the external centers as well as the Paul-Ehrlich Institute; the study was conducted according to the ethical principles of the Declaration of Helsinki. Patients' written informed consent was obtained to publish the data of the study.

Treatment and followup. Patients fulfilling inclusion criteria were randomized into 3 different arms and observed for 1 year. In arm 1 (control), all DMARD treatments remained unchanged. In arm 2 (tapering), all DMARD treatments were reduced by 50%. In arm 3 (tapering and stopping), all DMARD treatments were reduced by 50% for the first 6 months and then stopped for a further 6 months. Detailed mode of tapering of the individual drugs has been described elsewhere[6]. Primary efficacy variable was disease activity, as measured by DAS28 using ESR, which was assessed at baseline and after 3, 6, 9, and 12 months. Relapse was defined as DAS28-ESR ≥ 2.6. Further details on study procedures and collected demographics as well as disease-related variables are shown elsewhere[6].

Serum analyses. ACPA status was assessed in baseline serum samples of 146 RETRO patients. ACPA were measured by a commercial anticyclic citrullinated peptide 2 antibody test based on nephelometry (Beckmann Coulter). Cutoff value was 7 IU/ml. MBDA was assessed by commercial Vectra DA test (Crescendo Biosciences). Vectra DA includes 12 inflammation markers: epidermal growth factor, vascular endothelial growth factor A, interleukin 6, serum amyloid A, C-reactive protein (CRP), vascular cell adhesion molecule 1, matrix metalloproteinase 1 (MMP-1), MMP-3, tumor necrosis factor (TNF) receptor 1, human cartilage glycoprotein 39, leptin, and resistin. Detailed measurement is described elsewhere[10]. Based on the serum levels of these markers, a score (MBDA) is calculated as described previously[10]. The MBDA cutoff value for low inflammatory disease activity is 30 units; 30–44 units are defined as moderate disease activity and over 44 units means high disease activity. MBDA scores have been used to measure disease activity in RA[11,12,13,14].

Treatment cost calculation. At every study visit (baseline, months 3, 6, 9, and 12), direct treatment costs were calculated for each patient. Calculations included cDMARD, bDMARD, and corticosteroids. Other medication was not taken into consideration. Also, indirect costs (e.g., consultation, hospitalization, physiotherapy) were not considered. Drug costs (in euros) were based on the German drug directory and provide real-life values for each patient. Further distinctive features such as contracts with health insurance companies were not taken into account. Costs for the MBDA and ACPA testing were included in baseline costs.

Statistical analysis and risk stratification algorithm. We performed an interim analysis of patients who completed the 12-month study period. With

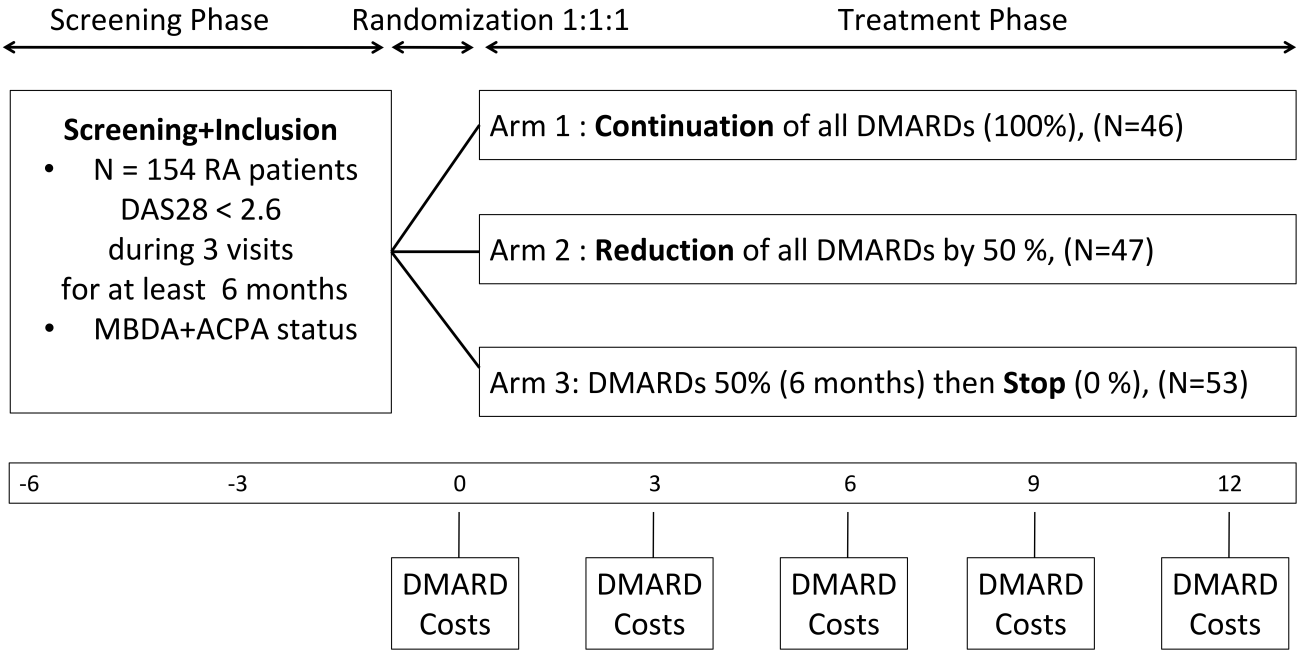

Figure 1. RETRO study design. Prospective randomized controlled trial with 3 treatment arms and 146 patients enrolled. Patients showed DAS28-ESR of < 2.6 for more than 6 months and were randomized into the 3 study arms (continuation, tapering, stop). ACPA and MBDA status were measured at baseline. Treatment costs were calculated with every study visit every 3 months. Patients were followed over 1 year. RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; DAS28-ESR: 28-joint count Disease Activity Score using erythrocyte sedimentation rate; ACPA: anticitrullinated protein antibodies; MBDA: multibiomarker disease activity.

MBDA scores and ACPA previously having been shown to predict relapse of RA[7], we designed risk diagrams for RETRO study patients for disease relapse according to the following previously identified predictors: ACPA status (positive/negative), MBDA score (moderate to high/low), and study arm (control, tapering, stopping). Models were performed with stratification for ACPA status only (Model 1) as well as ACPA status combined with MBDA results (Model 2). For both models, cost reductions associated with successful tapering or stopping of DMARD were calculated. Patients with a relapse risk of more than 50% were excluded from cost calculation because a tapering approach in clinical practice is not feasible. Inferential comparisons of subgroups were calculated using the Kruskal-Wallis test for numerical variables and exact chi-square tests for nominal characteristics. IBM SPSS version 21 was used for the analyses, and p values ≤ 0.05 were considered statistically significant. All results are presented in mean ± SD if not stated otherwise.

RESULTS

Baseline characteristics. One-year followup data of 146 patients enrolled in the RETRO study were available. The patients were randomized 1:1:1 in the 3 different treatment arms: arm 1 (control, n = 46), arm 2 (tapering, n = 47), arm 3 (tapering and stopping, n = 53; Figure 1). Table 1 shows the baseline characteristics of patients. Mean age was 56.1 (± 1.061) years, mean disease duration 7.1 (± 0.588) years, and 56.8% (n = 83) were female. All patients were in sustained clinical remission with a mean DAS28-ESR score of 1.71 (± 0.056) at baseline. There were 79.5% of patients taking cDMARD treatment with methotrexate (n = 116), while 39.0% (n = 57) of patients were taking bDMARD, including TNF inhibitors (tocilizumab and abatacept). ACPA positivity was found in 56.2% (n = 82) and MBDA scores over 30 units in 43.2% of the patients (n = 63). The distribution of MBDA positivity differed significantly (p = 0.018) between the 3 treatment arms. Baseline characteristics were comparable in the 3 arms.

Risk stratification algorithms using MBDA and ACPA status. Figure 2 shows a risk diagram with only ACPA status as relapse predictor (Model 1). Relapse risk was moderate in ACPA-negative patients when tapering (30%) or stopping (41.7%) DMARD treatment. For ACPA-positive patients, relapse risk was higher when tapering (48.1%) or stopping (65.52%) DMARD treatment. Figure 3 shows a risk diagram in which ACPA status was used in conjunction with MBDA score as relapse predictor (Model 2). Relapse risk for patients with double negativity (ACPA–, MBDA < 30) was 33.3% in patients who tapered treatment and even lower in patients who subsequently stopped treatment (11%). With either single positivity for ACPA or MBDA, relapse risk increased with little difference among ACPA and MBDA single positives. Patients with double positivity showed the highest risk for relapse, with 75% of patients in the tapering group and 81.2% of patients who tapered and subsequently stopped treatment.

Treatment costs. We defined patients who did not flare as successfully tapered and calculated their saved costs for cDMARD and bDMARD. Table 2A and Table 2B show the

Table 1. Baseline characteristics.

Characteristics	Total, n = 146	Control Arm 1, n = 46	Tapering Arm 2, n = 47	Stopping Arm 3, n = 53	p
Age, yrs	56.12	55	56.77	56.51	0.773
Female	56.8 (83)	52.2 (24)	57.4 (27)	60.4 (32)	0.710
Disease duration, yrs	7.1	7.2	7.3	6.8	0.330
Remission duration, mos	18.9	18.2	18.6	22.6	0.362
DAS28	1.71	1.66	1.61	1.85	0.136
RAID	1.19	1.19	0.96	1.36	0.529
Methotrexate use	79.5 (116)	80.4 (37)	76.6 (36)	81.1 (43)	0.838
bDMARD use*	39.0 (57)	34.8 (16)	44.7 (21)	37.7 (20)	0.602
Glucocorticoid use	23.3 (34)	26.1 (12)	23.4 (11)	20.8 (11)	0.822
Other cDMARD use**	13.7 (20)	13.0 (6)	12.8 (6)	15.1 (8)	0.933
RF-positive	56.2 (82)	45.7 (21)	66.0 (31)	56.6 (30)	0.142
ACPA-positive	56.2 (82)	56.5 (26)	57.4 (27)	54.7 (29)	0.961
MBDA-positive	43.2 (63)	34.8 (16)	34.0 (16)	58.5 (31)	**0.018**

Data are given as means or % (n). Values in bold face are statistically significant. Tumor necrosis factor inhibitors: * tocilizumab, abatacept; ** leflunomide, sulfasalazine, hydroxychloroquine. DAS28: 28-joint count Disease Activity Score (using erythrocyte sedimentation rate); RAID: Rheumatoid Arthritis Impact of Disease questionnaire; bDMARD: biological disease-modifying antirheumatic drugs; cDMARD: conventional DMARD; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; MBDA: multibiomarker disease activity.

distribution of treatment costs and their reduction in the 3 study arms in relation to risk predictors. Direct treatment costs for double-negative and single-positive groups (n = 41) would have been €372,245.16 for full-dose treatment over 1 year. Tapering and stopping DMARD in these low-risk relapse groups allowed a reduction of €219,712.03 in drug costs, which leads to an average cost reduction of €5358.83 per patient. There was no difference in treatment costs using ACPA or MBDA as first-order risk factors. When using only ACPA status for relapse prediction, overall cost reduction was lower with €184,580.00 and an average cost reduction of €4394.76 per patient with an overall higher relapse risk.

DISCUSSION

Achieving sustained remission with DMARD treatment has become a realistic goal in the treatment of RA. Several studies have addressed DMARD tapering in patients with RA in sustained DAS28 remission and low disease activity[4,15,16,17] and DMARD tapering has also been implemented in EULAR and ACR guidelines[18,19]. While it is clear that DMARD tapering is only feasible in patients with completely absent or very low signs and symptoms of disease[4], the question arises as to which patients can successfully taper or even stop DMARD treatment. The role of markers that increase or decrease the likelihood for disease relapse in patients tapering DMARD is of interest, because only some patients with RA can maintain remission after tapering the drugs. ACPA and MBDA are of interest in this respect, because ACPA status has no relation and MBDA only limited relation to clinical disease activity in RA[20]. Hence, some patients with RA in stable remission are characterized by positive ACPA and/or signs of biochemical disease activity reflected by moderate to high MBDA scores. Our previous data revealed that positive ACPA status and moderate/high MBDA scores predict the relapse risk in patients tapering DMARD[7].

In addition to the identification of patients able to taper treatment, economic considerations also come into focus[21,22,23,24]. This is largely because bDMARD costs are high, and successful tapering and stopping of these drugs in patients with RA in remission leads to a substantial reduction in DMARD costs. Importantly, drug costs have been shown to affect the treatment decisions of rheumatologists[5]. Today, with more effective and accessible DMARD to treat RA, potential overtreatment of patients with RA in remission may deserve recognition equal to that given to potential undertreatment of patients not in remission. Barnabe and colleagues stated that sustained remission can lead to decreased healthcare service use[25]. Michaud and colleagues analyzed the outcome and costs of using MBDA testing to improve the assessment of disease activity and subsequent changes in treatment decisions and showed that using MBDA score can reduce costs in patients with RA as well as improve their functional status[26].

Our present study shows that tapering or stopping DMARD achieves savings of direct healthcare costs, if the likelihood for relapse is low and the patients can permanently stay on a tapered DMARD regimen or could even stop treatment. RA patients with a low risk for relapse are at risk for overtreatment, while in those with high risk for relapse, tapering or even stopping DMARD treatment is not a feasible option. Our data show that overtreatment can be prevented and costs can be saved if tapering is performed in RA patients with low relapse risk based on ACPA and MBDA status. Such an approach can combine the interests of patients (safety, overtreatment), rheumatologists (personalized medicine), and health insurance (costs). For obvious reasons, prediction of relapses based on MBDA and ACPA cannot be 100% correct

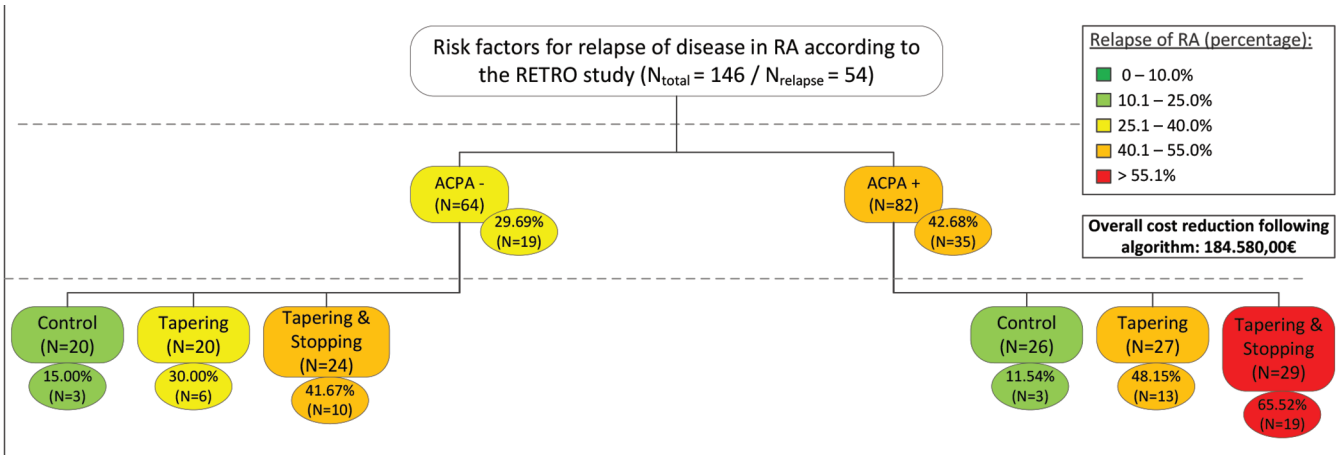

Figure 2. Relapse risk stratification using ACPA status only (Model 1). Green = low relapse risk (< 25% over 1 yr); yellow/orange = moderate relapse risk (26–55% over 1 yr); red = high relapse risk (> 55% over 1 yr). ACPA: anticitrullinated protein antibodies.

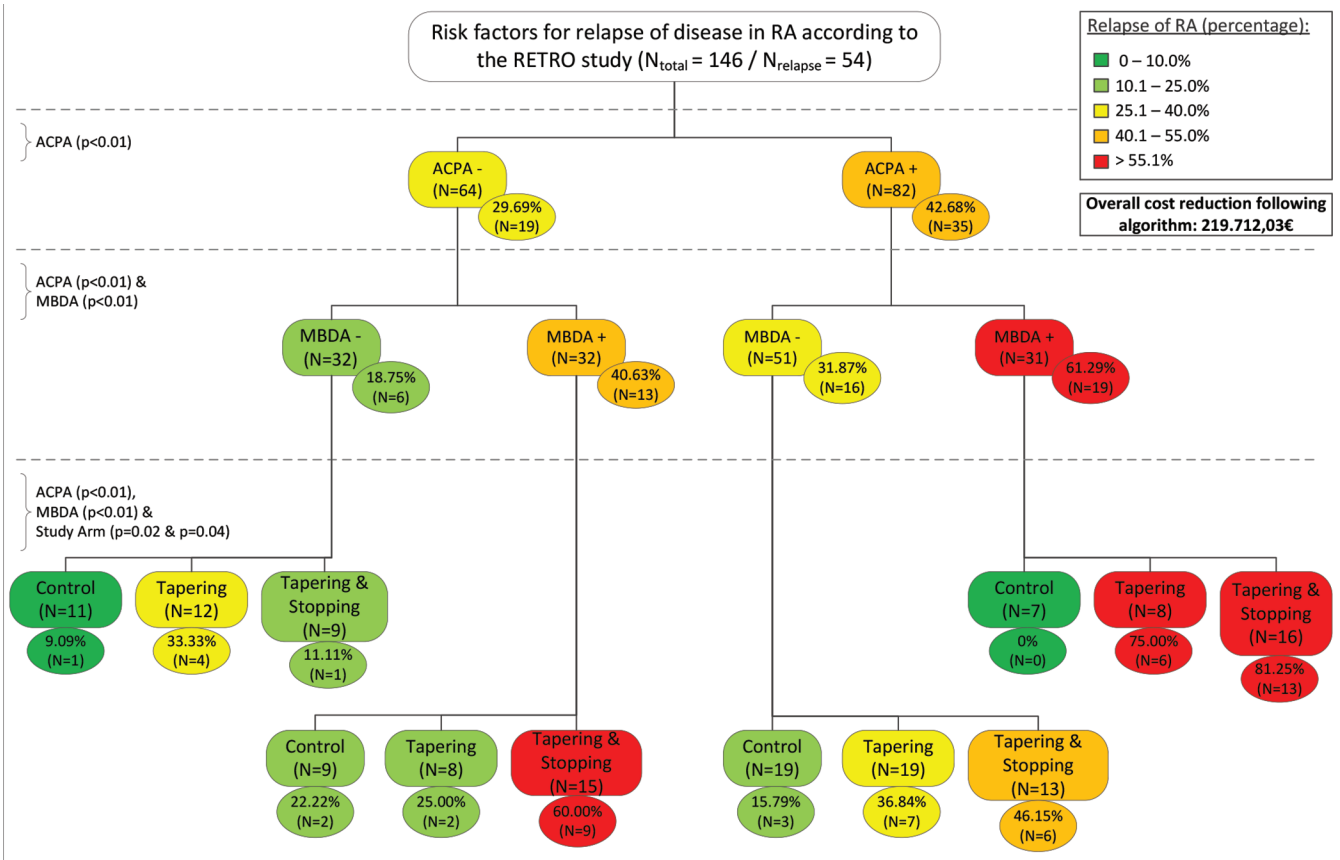

Figure 3. Relapse risk stratification using ACPA status combined with MBDA score (Model 2). Green = low relapse risk (< 25% over 1 yr); yellow/orange = moderate relapse risk (26–55% over 1 yr); red = high relapse risk (> 55% over 1 yr). RA: rheumatoid arthritis; ACPA: anticitrullinated protein antibodies; MBDA: multibiomarker disease activity.

on the individual patient's level. Hence, it has to be taken into account that even the combination of negative ACPA and low MBDA is no absolute guarantee against relapse, and the combination of positive ACPA and moderate/high MBDA is no absolute prediction of relapse.

It should be mentioned that cost reductions in DMARD reported in our study refer to prices of DMARD in Germany. Hence, the absolute numbers of DMARD savings may vary from country to country based on actual drug costs, the frequency of biosimilars used, and the presence

Table 2A. Cost reduction adapted to risk factors for relapse: model based on ACPA status only.

Arms	ACPA–	ACPA+	Total
Arm 1 (Control)	BL = €128,302.32 M12 = €128,302.51 – €0* (n = 17)	BL = €209,984.76 M12 = €209,984.76 – €0* (n = 23)	BL = €338,287.08 M12 = €338,287.27 – €0* (n = 40)*
Arm 2 (Tapering)	BL = €92,962.44 M12 = €44,436.58 **– €48,525.86** (n = 14)	BL = €222,054.56 M12 = €114,116.31 **– €107,938.25** (n = 14)	BL = €315,017.00 M12 = €158,552.89 **– €156,464.11** (n = 28)
Arm 3 (Stopping)	BL = €39,585.12 M12 = €11,469.26 **– €28,115.86** (n = 14)	BL = €49,231.20 M12 = €13,883.65 – €35,347.55** (n = 10)	BL = €39,585.12 M12 = €11,469.26 **– €28,115.86** (n = 14)
All			BL = €354,602.12 M12 = €170,022.12 **– €184,580.00** (n = 42)

Table 2B. Cost reduction adapted to risk factors for relapse: model based on ACPA status combined with MBDA score.

Arms	ACPA–/MBDA–	ACPA–/MBDA+	ACPA+/MBDA–	MBDA+/ACPA+	Total
Arm 1 (Control)	BL = €80,286.80 M12 = €80,286.80 – €0* (n = 10)	BL = €64,853.52 M12 = €64,853.52 – €0* (n = 7)	BL = €159,185.88 M12 = €159,185.88 – €0* (n = 16)	BL = €73,568.88 M12 = €73,568.88 – €0* (n = 7)	BL = €377,895.08 M12 = €377,895.08 – €0* (n = 40)
Arm 2 (Tapering)	BL = €70,839.24 M12 = €27,619.32 **– €43,219.92** (n = 8)	BL = €35,983.20 M12 = €16,817.20 – €**19,166.00** (n = 6)	BL = €189,480.00 M12 = €91,013.56 **– €98,466.44** (n = 12)	BL = €46,434.56 M12 = €23,102.75 – €23,331.81** (n = 2)	BL = €296,302.44 M12 = €135,450.08 **– €160,852.36** (n = 26)
Arm 3 (Stopping)	BL = €42,208.32 M12 = €9446.40 **– €32,761.92** (n = 8)	BL = €11,236.80 M12 = €1499.06 – €9737.74** (n = 6)	BL = €33,734.40 M12 = €7636.65 **– €26,097.76** (n = 7)	BL = €24,406.80 M12 = €6247.00 – €18,159.80** (n = 3)	BL = €75,942.72 M12 = €17,083.05 **– €58,859.67** (n = 15)
All					BL = €372,245.16 M12 = €152,533.13 **– €219,712.03** (n = 41)

Values in bold face are absolute saved costs. * No cost reduction, owing to study design. ** No cost reduction, owing to high relapse risk. BL: baseline assessment at start of tapering; M12: Month 12 followup; ACPA: anticitrullinated protein antibodies; MBDA: multibiomarker disease activity.

of insurance or pharmacy contracts regulating DMARD prices. Nonetheless, the concept that tapering and stopping DMARD in a low-relapse risk population is cost-effective seems to be generalizable. Further, it needs to be mentioned that data are based on a small patient cohort, and new MBDA cutoffs adjusted for age and weight have not been taken into account[27]. Another limitation of our study is that indirect costs were not analyzed; they can sometimes be substantially higher than direct costs[28]. Further, we analyzed patients in DAS28 remission, which at first sight contrasts with the ACR guideline stating that patients' medication should not be tapered unless the patient is in ACR/EULAR remission[19]. Our data suggest that tapering can be successful in a fraction of patients who are in DAS28-ESR remission. Also, when analyzing the subset of patients fulfilling the Boolean remission criteria at entry, MBDA remained as an independent predictor for relapse ($p = 0.01$). However, in the subset of patients fulfilling SDAI remission at entry, MBDA lost its independent prediction for relapse ($p = 0.24$), which is most likely because numerical CRP values are included in both Simplified Disease Activity Index (SDAI) and MBDA scores, and thus a smaller number of patients show elevated MBDA scores in SDAI remission.

Our study presents an approach toward cost-effective stratified DMARD tapering. It addresses the current challenges in handling stable remission in patients with RA, the possibility of a biomarker-based stratified DMARD tapering approach, and the reduction in DMARD costs resulting from such a concept.

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