Early treatment intensification induces favourable radiographic outcomes according to predicted *versus* observed radiographic progression in early rheumatoid arthritis: a subanalysis of the randomised FIN-RACo and NEO-RACo trials

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Abstract

Objective

Predicted versus observed radiographic progression in early rheumatoid arthritis (POPeRA) was applied to demonstrate how various treatment modalities affect and potentially minimise radiographic progression over time.

Methods

The POPeRA method utilises the baseline radiographic score and patient-reported symptom duration to predict radiographic outcomes. It was applied at baseline, 2, and 5 years to patients with eRA from the randomised Finnish RA Combination trial (FIN-RACo) (n=144) and New Finnish RA Combination Therapy (NEO-RACo) (n=90) trials. For FIN-RACo, patients were randomised either to a single DMARD (sulfasalazine, with or without prednisolone) or to combination therapy (methotrexate+sulfasalazine+hydroxychloroquine, i.e. triple therapy, with prednisolone). In NEO-RACo, all patients were assigned intensified combination therapy (including 7.5 mg prednisolone/day) plus a randomised 6-month induction of either placebo or anti-TNF treatment (infliximab).

Results

In FIN-RACo, combination versus monotherapy resulted in superior outcomes in the change from predicted progression over 2 and 5 years (mean 35.7% reduction vs. -32.9%, a worsening from predicted, p=0.001; 34.2% vs. -17.8%, p=0.003, respectively). In NEO-RACo, combination+anti-TNF induction led to significantly greater reductions from predicted progression than combination+placebo, both at 2 and 5 years of follow-up (98.5% vs. 83.4%, p=0.005; 92.4% vs. 82.5%, p=0.027, respectively). Importantly, anti-TNF add-on led to superior reductions from predicted among RF-positive patients (2 years: 97.4% vs. 80.4%, p=0.009; 5 years: 90.2% vs. 80.1%, p=0.030), but not among RF-negative patients.

Conclusion

These results confirm that conventional combination therapy in eRA has a long-term radiographic benefit versus monotherapy. Through POPeRA, it was made evident that anti-TNF induction therapy for 6 months further increases the long-term radiographic benefit of combination therapy in RF-positive patients.

Key words

rheumatoid arthritis, predictions and projections, radiography, antirheumatic agents, biologics

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Introduction

Early treatment of rheumatoid arthritis (RA) (1, 2) with synthetic disease-modifying anti-rheumatic drugs (DMARDs) is well-established, and stratagems include early intensification of treatment with combination therapy (3-8) and treating-to-target (9, 10). A 'window of opportunity' for treatment of RA in its early form can range from approximately 3 months to 2 years from symptom onset (11, 12), and treatment with intensive conventional DMARDs or biologics beginning within this time frame offers valuable clinical and/or radiographic benefit over several years (13-21). Despite being established, the success of treating within a 'window of opportunity' with early, aggressive therapy needs to be made more clear in how it might *prevent* a significant amount of otherwise irreversible bone erosion.

We previously proposed a method to simulate bone damage over time as if patients were not on treatment in order to compare the relative radiographic efficacies of different treatments. This method – Predicted *vs.* Observed Radiographic Progression in early Rheumatoid Arthritis (POPeRA) – has previously confirmed the relative radiographic efficacy of conventional DMARDs and anti-tumour necrosis factor (anti-TNF) treatment (22, 23). POPeRA is comprised of two components; patient-reported symptom duration, as well as radiographic damage at baseline (BL) – which alone has been shown to be an independent long-term predictor of patient-related outcomes in RA (24). Symptom duration, however, allows for predicted scores at certain time points to be simulated. By comparing the changes from the predicted score for each therapy, POPeRA is thus capable of delineating whether or not the 'window of opportunity' could perhaps be a more successful medical strategy for particular therapies than others. In order to demonstrate how various treatment modalities affect and potentially minimise radiographic progression over time, in this study we applied the POPeRA method to the randomised Finnish Rheumatoid Arthritis Combination trial (4) (FIN-RACo, combination *vs.* single) as well as the NEO-RACo trial (20) (combination + anti-TNF *vs.* combination + placebo) – both of which demonstrated that early treatment intensification is capable of hindering bone erosions several years after initiation of treatment.

Methods

The FIN-RACo and NEO-RACo trials

The POPeRA method was applied to 144/160 (90%) and 90/91 (98.9%) patients with eRA who had available radiographic scores at all time points from the FIN-RACo and NEO-RACo trial 5-year follow-ups, respectively. The Larsen score (FIN-RACo) and Sharp-van der Heijde score (SHS) (NEO-RACo) was available at BL, 2, and 5 years. FIN-RACo was a 2-year multicentre open-label randomised trial, previously described in detail (4), where patients were randomised either to a single DMARD (all starting with sulfasalazine; 60% had prednisolone as required) or to more intensive DMARD combination therapy (all starting with triple therapy: methotrexate + sulfasalazine + hydroxychloroquine, and prednisolone). Non-steroidal anti-inflammatory drugs, intra-articular glucocorticoid injections, and supplementary folic acid according to the physician's judgment were allowed in both treatment groups, and the protocol was flexible for dose adjustments to mimic clinical practice, including increasing or tapering doses. In cases of toxicity or non-response in either group, other conventional DMARDs could be used as substitutes.

NEO-RACo was a 2-year multicentre placebo-controlled randomised trial (20) where all patients were assigned to intensified FIN-RACo combination protocol (including 7.5 mg of prednisolone per day) plus a randomised 6-month induction of either placebo or anti-TNF treatment (infliximab). All patients received folic acid, calcium, and vitamin D3 supplements; and intra-articular glucocorticoids were injected in swollen joints. If methotrexate was not tolerated it could be switched to subcutaneous injection. A DMARD would be changed due to toxicity, and/or if inefficacy was present on maximum doses for 3 months. For both trials, treatment was targeted to remission and became

unrestricted after 2 years, and radiographic follow-up was done at 5 years. The methods of radiographic analysis have been previously described in detail (4, 20).

The FIN-RACo and NEO-RACo trials were conducted in accordance with the Declaration of Helsinki and their protocols were approved by the national health authorities (The Finnish Medicines Agency, FIMEA). The ethics committees in all 18 participating sites of the FIN-RACo trial approved FIN-RACo (see Acknowledgements for additional information), and the NEO-RACo trial was approved by the Internal medicine ethical committee of the Hospital District of Helsinki and Uusimaa. All patients gave written informed consent prior to study inclusion. FIN-RACo study registration: Current Controlled Trials, ISRCTN18445519 (registered 13/11/2009); NEO-RACo study registration: clinicaltrials.gov, NCT00908089 (registered 22/05/2009).

Radiographic model

POPeRA predicts radiographic outcomes over time as if patients were not on treatment. The predicted progression is derived from an inferred progression rate (BL radiographic score divided by the patient-reported symptom duration in months before BL), which is then multiplied by the time point of the radiograph plus the BL score to achieve the predicted score (23). As a positive score is required at BL, all patients had their radiographic scores increased by a value of 1 for all time points in order to be included in the model.

Four sensitivity analyses were conducted for model verification, which have been performed and explained previously (23). These analyses either included all patients but with imputed zeroes instead of an increase of all values by 1; only patients who had any erosion (Larsen or SHS >0) over 5 years (with or without imputed zeroes); or only patients with any erosion already at BL.

Statistical analyses

Non-parametric statistical analyses, including the Mann-Whitney U-test, Pearson's χ^2, and the Kruskal-Wallis test, were performed on IBM SPSS v. 22.0. Comparisons included testing for differences in patient characteristics, radiographic scores, and percentage reduction from the predicted score across all treatment regimens. Two-tailed *p*-values were interpreted as significant when below the 0.05 level.

Results

Patient characteristics

In the FIN-RACo and NEO-RACo trials (Table I), the distribution of patients among all treatment groups did not differ by age, sex, symptom duration, rheumatoid factor (RF) positivity, or BL erosions. Anti-cyclic citrullinated peptide antibody status was unavailable. As previously reported (14, 21), the combination group had significantly less radiographic progression at 2 and 5 years than monotherapy, though no absolute radiographic differences were found between the combination + anti-TNF or combination + placebo arms (Table I).

Patients positive for RF in both trials (FIN-RACo, n=102 *vs*. 42; NEO-RACo, n=67 *vs*. 23) had more radiographic progression at 2 and 5 years than RF-negative patients: FIN-RACo: median 12.0 [IQR 3.8, 19.3] *vs*. 4.0 [1.0, 17.5], *p*=0.022; 21.0 [9.0, 32.3] *vs*. 11.0 [1.0, 22.8], *p*=0.002, respectively; NEO-RACo: 2.0 [1.0, 5.0] *vs*. 1.0 [1.0, 3.0], *p*=0.052; 3.0 [1.0, 9.0] *vs*. 1.0 [1.0, 4.0], *p*=0.046, respectively.

Predicted vs. observed radiographic progression

In FIN-RACo, combination *vs*. monotherapy resulted in superior outcomes in the change from predicted progression over 2 and 5 years (mean 35.7% reduction *vs*. -32.9%, a worsening from predicted, *p*=0.001; 34.2% *vs*. -17.8%, *p*=0.003, n=72, respectively; Table II, Fig. 1). Patients positive for RF (n=102) had significantly worse changes from predicted at 2 and 5 years than RF-negative patients (n=42) (-13.6% [SD ±189.9] *vs*. 38.1% [±137.8], *p*=0.035; -6.7% [±161.2] *vs*. 44.3% [±134.0], *p*=0.002, respectively). Superiority

Table I. Patient characteristics from the FIN-RACO and NEO-RACO trials.

Outcomes	Combo (n=72)	Single (n=72)	*p*-value[1]	Combo + aTNF (n=44)	Combo + PBO (n=46)	*p*-value[1]
Age (Y)*	48.0 (39.3, 52.8)	50.0 (40.3, 56.8)	*p*=0.184	51.0 (44.5, 54.0)	47.5 (36.0, 55.0)	*p*=0.472
Sex (F)†	43 (59.7%)	49 (68.1%)	*p*=0.298[2]	29 (63.0%)	32 (72.7%)	*p*=0.326[2]
Duration (months)*	6.0 (4.0, 9.8)	7.0 (4.0, 10.0)	*p*=0.582	4.0 (2.0, 5.8)	4.0 (3.0, 6.0)	*p*=0.516
RF Positive†	53 (73.6%)	49 (68.1%)	*p*=0.463[2]	33 (71.7%)	34 (77.3%)	*p*=0.547[2]
Radiograph baseline*	1.0 (1.0, 5.8)	3.0 (1.0, 8.5)	*p*=0.349	1.0 (1.0, 3.0)	1.0 (1.0, 3.3)	*p*=0.593
Radiograph 2 years*	5.0 (1.0, 16.5)	14.5 (5.0, 23.0)	*p*=0.001	1.0 (1.0, 4.0)	2.5 (1.0, 5.3)	*p*=0.226
Predicted 2 years*	9.0 (7.0, 22.5)	10.0 (6.25, 35.5)	*p*=0.435	13.5 (7.25, 26.5)	9.5 (7.0, 25.75)	*p*=0.194
Radiograph 5 years*‡	12.0 (3.3, 27.3)	25.0 (11.5, 34.5)	*p*=0.001	2.0 (1.0, 5.8)	3.0 (1.0, 9.0)	*p*=0.302
Predicted 5 years*‡	21.0 (13.75, 48.0)	22.0 (13.25, 70.5)	*p*=0.445	31.5 (16.25, 62.5)	21.5 (16.0, 61.75)	*p*=0.176

Combo: combination arm, intention-to-treat (FIN-RACo), Single: monotherapy arm, intention-to-treat (FIN-RACo); Combo + aTNF: combination + anti-TNF arm, intention-to-treat (NEO-RACo), Combo + PBO: combination + placebo arm, intention-to-treat (NEO-RACo). 1. Mann-Whitney U-test, unless otherwise stated, 2. Pearson's χ^2. All the following outcomes were reported as the median, followed by the interquartile range in parentheses: *age in years, patient-reported symptom duration in months before baseline (BL), and the observed or predicted Larsen (FIN-RACo) or Sharp-van der Heijde (NEO-RACo) radiographic score at BL, 2, and 5 years, respectively. The following were reported as proportions: †sex (percent female) and percent rheumatoid factor (RF) antibody positive. ‡Treatments in all groups became unrestricted after 2 years. All radiographic scores are represented with an increase of 1 unit, as this was required to include all patients in the model.

Table II. Percent reduction of predicted radiographic progression from the FIN-RACO and NEO-RACO trials.

Radiographic outcomes	Combo (n=72)	Single (n=72)	*p*-value[1]	Combo + aTNF (n=44)	Combo + PBO (n=46)	*p*-value[1]
2 years	35.7 (±127.4)	-32.9 (±211.6)	*p*=0.001	98.4 (±7.6)	83.4 (±40.6)	*p*=0.005
Median (IQR)	94.2 (30.8, 100.0)	47.8 (-83.0, 98.4)		100.0 (100.0, 100.0)	100.0 (82.6, 100.0)	
5 years*	34.2 (±127.7)	-17.8 (±175.4)	*p*=0.003	92.4 (±19.8)	82.5 (±41.3)	*p*=0.027
Median (IQR)	80.0 (21.7, 100.0)	47.2 (-62.5, 86.0)		100.0 (96.3, 100.0)	98.2 (75.0, 100.0)	

Combo: combination arm, intention-to-treat (FIN-RACo), Single: monotherapy arm, intention-to-treat (FIN-RACo); Combo + aTNF: combination + anti-TNF arm, intention-to-treat (NEO-RACo), Combo + PBO: combination + placebo arm, intention-to-treat (NEO-RACo). [1]Mann-Whitney U-test. Results are reported as the mean reduction in percent of the predicted Larsen (FIN-RACo) or Sharp-van der Heijde score (NEO-RACo), respectively, at 2 and 5 years with standard deviation in parentheses, or the median reduction in percent with the interquartile range (IQR) in parentheses. Negative values indicate a worsening from predicted. *Treatments in all groups became unrestricted after 2 years.

for combination *vs*. monotherapy was observed in both RF-positive and RF-negative patients (Table III). Both arms were capable of significantly hindering radiographic progression over 5 years; however, monotherapy did not appear to effectively reduce progression over 2 years (see Supplementary Table IVA). In NEO-RACo, combination + 6 months of anti-TNF therapy (n=44) led to significantly greater reductions from predicted progression than combination + placebo (n=46) both at 2 and 5 years of follow-up (98.5% *vs*. 83.4%, *p*=0.005; 92.4% *vs*. 82.5%, *p*=0.027, respectively; Table II, Fig. 2A). However, initial anti-TNF add-on treatment was superior only among RF-positive patients (n=34, 33, respectively): 2 years: 97.4% *vs*. 80.4%, *p*=0.009; 5 years: 90.2% *vs*. 80.1%, *p*=0.030 (Table III, Fig. 2B). Although the predicted scores among both arms did not differ statistically at 2 and 5 years among all patients (Table I, Fig. 2A) or among RF-positive patients (Fig. 2B), they appeared numerically different. Thus, an additional analysis was tested by applying the overall mean symptom duration (4.1 months) to all patients, which generated a new, average predicted slope (see Supplementary Figs. 2C-D). Applying the results in this manner led to comparable outcomes as above among all patients (combination + anti-TNF *vs*. combination + placebo: 2 years: 97.6% [±7.9] *vs*. 85.3% [±30.0], *p*=0.006; 5 years: 90.6% [±25.4] *vs*. 84.6% [±30.8], *p*=0.028), and also as above among the RF-positive patients (2 years: 96.8% [±8.6] *vs*. 83.5% [±33.3], *p*=0.010; 5 years: 88.5% [±28.6] *vs*. 82.7% [±34.4], *p*=0.019, respectively). Overall, regardless of the modality, potential radiographic progression was hindered greatly over 2 and 5 years (see Supplementary Table IVB).

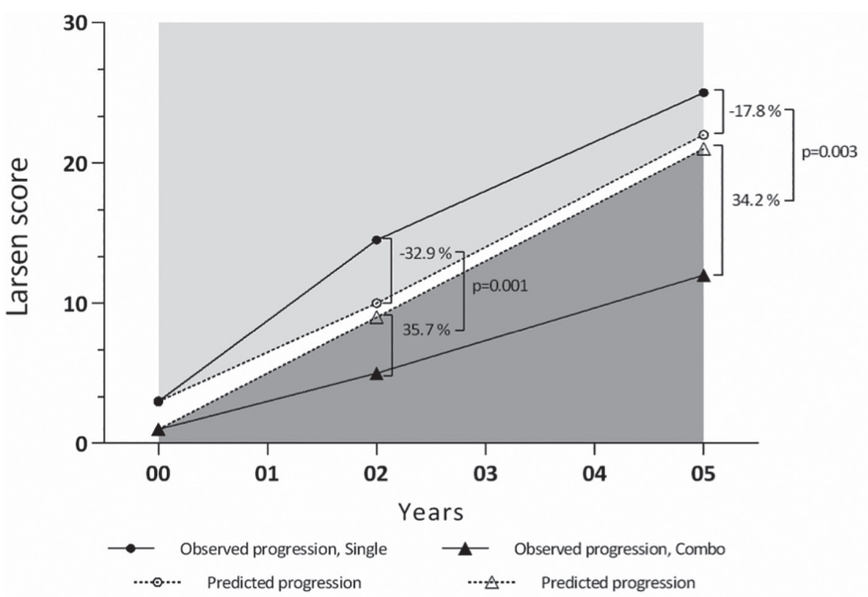

Fig. 1. Results from the FIN-RACO trial.
Combo: combination arm, intention-to-treat (n=72), Single: monotherapy arm, intention-to-treat (n=72). Mann-Whitney U-tests were performed to compare the differences, as a result of therapy, in the percent change of the predicted scores of all patients. The mean percent change for all patients within each respective therapy is shown. The median predicted and observed Larsen scores are plotted at baseline (**00**), 2, and 5 years (**02** and **05**). Median scores for Combo, followed by interquartile range (not in the figure for graphical purposes) in parentheses: **00**: 1.0 (1.0, 5.8); **02**: predicted: 9.0 (7.0, 22.5), observed: 5.0 (1.0, 16.5); **05**: predicted: 21.0 (13.8, 48.0), observed: 12.0 (3.3, 27.3). Scores for Single: **00**: 3.0 (1.0, 8.5); **02**: predicted: 10.0 (6.3, 35.5), observed: 14.5 (5.0, 23.0); **05**: predicted: 22.0 (13.3, 70.5), observed: 25.0 (11.5, 34.5). Treatment in both groups became unrestricted after 2 years.

All sensitivity analyses confirmed the original findings above, in that superior outcomes were found in Combo *vs*. Single, or Combo + anti-TNF *vs*. Combo + placebo, respectively – except in the last sensitivity analysis with a smaller group of patients requiring BL erosions (initial radiographic score >0), where, at 2 or 5 years, significant differences were not found (FIN-RACO: n=73, NEO-RACo: n=37; results not shown). However – although RF positivity did not distinguish a response in Combo *vs*. Single – we found in this last sensitivity analysis that Combo + initial anti-TNF treatment still provides a lasting benefit at 5 years for RF-positive patients (n=16 *vs*. 13, median 100.0% [IQR 95.2, 101.9] *vs*. 94.2% [81.3, 98.7], *p*=0.036).

Discussion

We demonstrated that DMARDs in combination effectively suppress potential radiographic progression in patients with eRA. We also showed that conven-

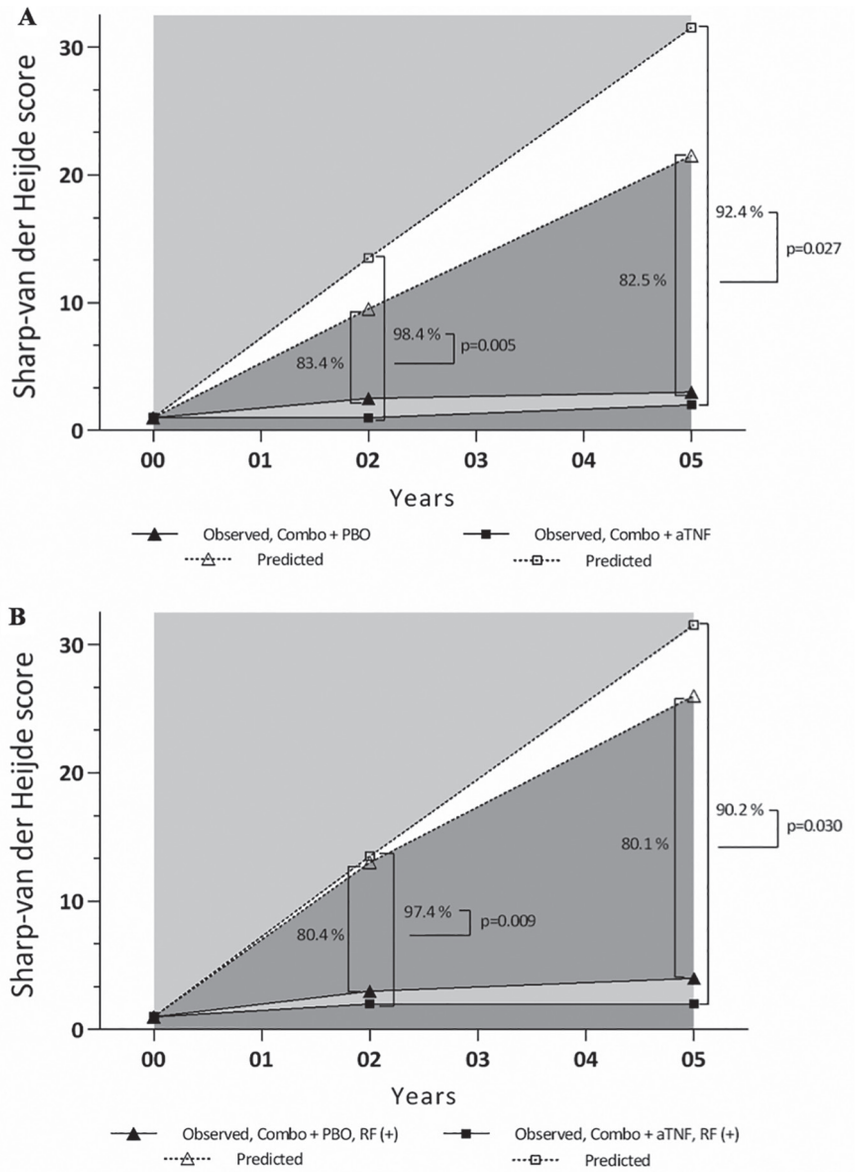

Fig. 2. Results from the NEO-RACO trial.
Combo + aTNF: combination + anti-TNF arm, intention-to-treat (n=44), Combo + PBO: combination + placebo arm, intention-to-treat (n=46). Mann-Whitney U-tests were performed to compare the differences, as a result of therapy, in the percent change of the predicted scores of all patients. The mean percent change for all patients treated by each respective therapy is shown. The median predicted and observed Sharp-van der Heijde scores are plotted at baseline (**00**), 2, and 5 years (**02** and **05**). Treatment in all groups became unrestricted after 2 years. Predicted slopes might not appear linear all throughout due to medians being plotted.
A. All patients (n=90). Median scores for Combo + aTNF, followed by interquartile range (not in the figure for graphical purposes) in parentheses: **00**: 1.0 (1.0, 3.0); **02**: predicted: 13.5 (7.3, 26.5), observed: 1.0 (1.0, 4.0); **05**: predicted: 31.5 (16.3, 62.5), observed: 2.0 (1.0, 5.8). Scores for Combo + PBO: **00**: 1.0 (1.0, 3.3); **02**: predicted: 9.5 (7.0, 25.8), observed: 2.5 (1.0, 5.3); **05**: predicted: 21.5 (16.0, 61.8), observed: 3.0 (1.0, 9.0).
B. Patients rheumatoid factor (RF) positive (+) (n=67). Median scores for Combo + aTNF (n=34), followed by interquartile range (not in the figure for graphical purposes) in parentheses: **00**: 1.0 (1.0, 3.3); **02**: predicted: 13.5 (7.0, 31.5), observed: 2.0 (1.0, 5.0); **05**: predicted: 31.5 (16.0, 73.5), observed: 2.0 (1.0, 7.3). Scores for Combo + PBO (n=33): **00**: 1.0 (1.0, 4.5); **02**: predicted: 13.0 (7.0, 35.0), observed: 3.0 (1.0, 6.0); **05**: predicted: 26.0 (16.0, 80.0), observed: 4.0 (1.0, 10.0).

tional combination therapy has more beneficial long-term effects than monotherapy, regardless of RF status. Further intensification of combination therapy with 6 months of anti-TNF therapy can provide an additional radiographic benefit over several years among all patients with eRA. However, this beneficial effect was observed exclusively in RF-positive patients. These results confirm the original and follow-up findings from the FIN-RACo trial, where it was found that combination *vs*. monotherapy led to more cases of remission and less radiographic damage (4, 14). In the original findings from the NEO-RACo trial, although combination + initial anti-TNF therapy led to more favorable radiographic outcomes over combination + placebo at 2 years (20), it was not seen at 5 years (21) – and the difference in actual radiographic progression was minimal across the groups. Our study, however, further illustrates the NEO-RACo findings in that we have now demonstrated that combination + anti-TNF therapy led to a greater delay in radiographic progression both at 2 and 5 years than combination + placebo, but the beneficial effect of initial biologic treatment was significant only among RF-positive patients.

There are potential weaknesses or limitations in this study. Symptom duration relies upon the judgment and accuracy of the patients who had informed their physicians of this key variable, which may or may not be precise. Secondly, anti-cyclic citrullinated peptide antibody status – an important potential predictor of radiographic progression (25-28) – was unavailable for these patients and should be tested with POPeRA in future datasets. Also, predicted progression through POPeRA could be an overestimation of radiographic progression provided that the patients were not on treatment, as progression is not precisely linear (22, 23, 29) – although relatively accurate concerning groups rather than individuals (30). We discovered that the predicted progression was more close to the observed progression in FIN-RACo, and the observed scores appeared worse than predicted for the monotherapy arm. An explanation to this may be the fact that the maximum allowed symptom duration was 24 months, instead of 12 months as in NEO-RACo – a longer duration can lessen the predicted slope – and/or it may be a potential limitation to utilise the Larsen score in predicting progression. Our opinion is that these patients certainly benefited more from monotherapy than the simulation of receiving no treatment, as the median reductions

Table III. Percent reduction of predicted radiographic progression from the FIN-RACO and NEO-RACO trials, divided by rheumatoid factor.

	Rheumatoid factor (+)			Rheumatoid factor (-)		
Radiographic outcomes	Combo (n=53)	Single (n=49)	*p*-value[1]	Combo (n=19)	Single (n=23)	*p*-value[1]
2 years	21.1 (±143.1) 88.9 (-14.3, 100.0)	-51.2 (±225.7) 0.0 (-93.8, 77.5)	*p*=0.003	76.7 (±49.4) 100.0 (75.0, 100.0)	6.2 (±176.1) 91.7 (-25.0, 100.0)	*p*=0.114
5 years*	15.9 (±143.3) 60.0 (-2.2, 94.8)	-31.1 (±176.9) 37.8 (-86.7, 76.1)	*p*=0.047	85.2 (±35.0) 100.0 (80.0, 100.0)	10.4 (±172.7) 66.7 (10.0, 90.3)	*p*=0.002
Radiographic outcomes	Combo + aTNF (n=34)	Combo + PBO (n=33)	*p* value[1]	Combo + aTNF (n=10)	Combo + PBO (n=13)	*p* value[1]
2 years	97.4 (±8.0) 100.0 (92.6, 100.0)	80.4 (±46.2) 97.5 (82.0, 100.0)	*p*=0.009	101.6 (±5.4) 100.0 (100.0, 100.4)	91.0 (±20.2) 100.0 (75.0, 100.0)	*p*=0.343
5 years*	90.2 (±22.0) 100.0 (92.9, 100.0)	80.1 (±46.7) 96.7 (73.4, 100.0)	*p*=0.030	99.9 (±2.8) 100.0 (98.3, 100.0)	88.7 (±22.7) 100.0 (80.0, 100.0)	*p*=0.648

Patients distinguished as rheumatoid factor positive (+) or negative (-). Combo: combination arm, intention-to-treat (FIN-RACo), Single: monotherapy arm, intention-to-treat (FIN-RACo); Combo + aTNF: combination + anti-TNF arm, intention-to-treat (NEO-RACo), Combo + PBO: combination + placebo arm, intention-to-treat (NEO-RACo). [1]Mann-Whitney U-test. Results are reported as the mean reduction in percent of the predicted Larsen (FIN-RACo) or Sharp-van der Heijde score (NEO-RACo), respectively, at 2 and 5 years with standard deviation in parentheses, or the median reduction in percent with the interquartile range (IQR) in parentheses. Negative values indicate a worsening from predicted. *Treatments in all groups became unrestricted after 2 years.

from predicted for these patients at 2 and 5 years was approximately 47%, respectively. Several patients in this arm had a large worsening from predicted and the mean change was thus skewed, which should be kept in mind when interpreting these results (mean changes from predicted were included in the figures for graphical purposes). Overall, in accordance to the median, the majority of patients benefited from monotherapy. In this study, there was no non-responder group to be compared to the predicted progression as a proxy to determine its relative accuracy, but it has been previously determined that non-responders to several therapies most closely resemble a control group and have the most similar outcomes to predicted progression (22, 23). Finally, the POPeRA method could be applied to future datasets that involve important variables of interest with good positive predictive value, such as the multi-biomarker disease activity score (31) or smoking (32), each of which have been shown to be independent predictors of radiographic progression.

Although randomised clinical trials are not immune from practical or intrinsic limitations (33), the strengths in this study are that two randomised trials with a large sample of patients were each individually tested with the POPeRA method, leading not only to confirmation of the results of the original trials but adding further value. We believe that this method allows us to detect a difference that was not seen in the original analysis. It is clear that conventional combination therapy is a cost-effective regimen (34) and is at a large advantage to anti-TNF therapy (35, 36) in this sense, however, we have now elucidated that RF-positive patients with eRA may be suited to receive infusions of anti-TNF for half a year together with continuous treat-to-target conventional combination therapy – as, arguably, more potential damage can be prevented over 5 years. As always, the value that biologics may provide must be individually determined by each treating physician. It is vital to know that despite withdrawal of anti-TNF after 6 months, beneficial long-term outcomes while continuing on conventional combination therapy are apparent. In spite of the new radiographic results, the total potential benefits or harm that additional anti-TNF treatment may provide, chiefly among RF-positive patients, needs to be further evaluated. Studies now need to be done to determine, for example, the cost-effectiveness and safety of this option over continuous or step-down biological therapy.

Conclusions

These results confirm that conventional combination therapy in eRA has a long-term radiographic benefit versus monotherapy. Using the POPeRA method, the addition of anti-TNF induction therapy for 6 months was shown to further increase the long-term radiographic benefit of combination therapy in RF-positive patients.

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