REPORT

Using estimated yearly progression rates to compare radiographic data across recent randomised controlled trials in rheumatoid arthritis

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T his review is based on publications and presented abstracts from six randomised controlled trials (RCTs) in the treatment of rheumatoid arthritis assessing treatment effects on radiographic measures of disease progression. Each used the Sharp scoring method to assess changes in erosions and joint space narrowing from baseline.[1–3] These RCTs showed that the newly approved synthetic and biological disease modifying antirheumatic drugs, leflunomide, infliximab, etanercept, and Anakinra, were effective, and confirmed the efficacy of sulfasalazine and methotrexate in retarding disease progression.[4–13] Provided that sample sizes are adequate, randomisation within a protocol accounts for the heterogeneity of disease populations and yields linear progression rates over time.[14]

Each RCT enrolled a unique patient group with significantly different demographics and baseline disease characteristics across the trials, although well balanced within each protocol. Because of these population differences it is not appropriate to compare directly changes in total composite (Sharp) scores across trials. However, it is possible to compare the data if one uses an estimate of yearly progression of radiographic damage, based on prior progression, where patients have continued to receive previous treatment, or were untreated. This is obtained by dividing mean baseline composite scores for each treatment group by the mean reported disease duration (table 1).[15 16] This value can be used as a "benchmark," allowing rough numerical comparisons to observed change scores, but should not be used for statistical comparisons. Estimated progression rates are, of course, only estimates, limited by errors in dates of disease onset, and are less valid in patients with disease durations of ≤1 year. Table 1 illustrates that, despite certain common baseline demographics and disease characteristics, each protocol population in these recent RCTs had a unique estimated yearly progression rate.

All trials used the composite scoring method; the European interleukin 1 receptor antagonist (ILRa) monotherapy RCT included x rays of the hands and not the feet.[17 18] When comparing data across trials, these differences do not appear to be important because observed progression rates in all active treatment groups seem similar and numerically much less than estimated yearly progression rates. Mean changes in composite scores in the placebo treatment groups in three of the four recent RCTs met or exceeded estimated yearly progression rates for the trial groups, with one exception, the "Utilization of Leflunomide for the Treatment of Rheumatoid Arthritis" (ULTRA or US 301 trial), where 63% of patients initially assigned to placebo received active treatment for a mean of 7–8 months when 12 month follow up radiographs were performed.[4] Table 2 illustrates the good agreement between estimated yearly progression rates and observed change scores in placebo treatment groups in four RCTs including the leflunomide, methotrexate, and sulfasalazine comparisons, respectively (US 301 and MN 301), "Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy" (ATTRACT), and European IL1Ra monotherapy trials. This indicates that the estimated yearly progression rate at baseline may be useful when comparing radiographic data across RCTs.

In general, radiographic responses are poorly correlated with clinical improvements by American College of Rheumatology (ACR) response criteria or disease activity score, C reactive protein (CRP), or measures of physical function.[19 20] In longitudinal series, it is not until patients have 8–15 years of disease that we see correlations between evidence of radiographic damage and loss of physical function.[21]

Estimated yearly progression rates also best predict radiographic progression over 2–5 years of continued active treatment in the COBRA trial, when the two treatment groups

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Abbreviations: CRP, C reactive protein; IL1Ra, interleukin 1 receptor antagonist; RCTs, randomised controlled trials

Table 1	Baseline demographic and disease characteristics					
Variable	US 301[4 7]	MN 301[5 7]	MN 302[5 6]	ATTRACT[9]	ERA[10 13]	European IL1Ra[11 12]
Total No of patients	482	356	985	428	632	472
No in each treatment group	118–182	91–134	487–495	81–88	207–217	116–121
Mean age (years)	53–55	55–59	58	51–54	49–51	52–54
Mean disease duration (years)	6.5–7.0	5.7–7.6	3.7–3.8	9.2–11.6	≤1.0	3.7–4.3
≤2 Years' disease duration (%)	33–40	38–45	43–44	9–23*	100	NR
Mean DMARDs failed	0.8–0.9	0.8–1.0	1.1	3.0	0.5–0.6	NR
DMARD naive (%)	40–45	40–53	33–34	0	54–61	19–34
Baseline HAQ-DI	1.3	1.7–1.9	1.5	1.7–1.8	1.4–1.5	1.5–1.6
Baseline composite x ray scores	22.8–25.4	41.9–46.3	24.6–24.9	66.6–81.9	11.2–12.9	24.7–29.6
Estimated yearly progression	3.3–3.7†	5.7–8.1†	6.5–6.7†	6.4–8.0†	8.0–9.0†‡	6.3–7.4†

RF, rheumatoid factor; DMARDs, disease modifying antirheumatic drugs; CRP, C reactive protein; HAQ-DI, Health Assessment Questionnaire disease index; NR, not reported.
*% Of patients with ≤3 years' disease duration; †calculated from mean of baseline total Sharp scores divided by mean disease duration for each treatment group; ‡may be overestimated owing to mean disease duration of ≤1 year.

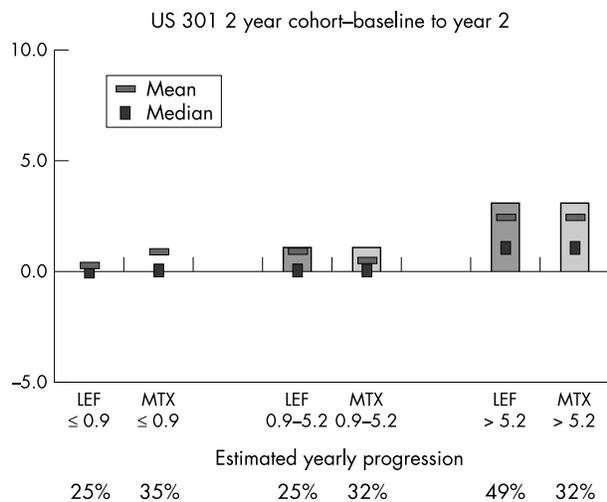**Table 2** Estimated yearly progression rates *v* observed changes in placebo treatment groups

Variable	US 301[7]	MN 301[7]	ATTRACT[9]	European IL1Ra[12]
Mean disease duration (years)	6.9	5.7	10.9	3.7
Baseline total composite score	25.4	46.2	81.9	27.4
Estimated 6 or 12 month progression rates at baseline	3.7	8.2*	7.7	7.4*
Observed yearly progression rates in placebo groups over 6 or 12 months	2.2	11.8*	7.0	7.0*

*Estimated annual progression rates are based on six months' treatment.

were divided into tertiles according to estimated yearly progression rates at baseline.[22] Medians and interquartile ranges of change in *x* ray scores over 2–5 years in the second and third tertiles in the sulfasalazine group, and in the third tertile in the COBRA group, were higher than in the first, indicating a continued benefit from treatment on radiographic progression with combination therapy (web extra fig W1). In the ATTRACT trial, progression over two years in the

infliximab + methotrexate groups combined showed medians of 0 across all three tertiles, compared with progressively higher median scores in each tertile in the placebo + methotrexate treatment group, again demonstrating the persistent benefit of combination therapy.[23] Similar differences in progression in the leflunomide and methotrexate groups in US 301 and MN 302/4 are evident over two years of treatment, with more progression in the third tertiles than first, and higher values in the protocol with the earlier disease group (MN 302/4) (figs 1 and 2).[6 24] Estimated rates of yearly progression at baseline, rather than rheumatoid factor, CRP, or other disease characteristics best predicted further damage.

In conclusion, sample sizes in recent RCTs have been sufficient to demonstrate linear radiographic progression rates over 2–5 years of continued treatment. Each protocol population is unique, with a unique estimated yearly radiographic progression rate. These estimated rates can serve as a "benchmark" to facilitate comparisons across RCTs, to allow better comparison of treatment associated effects in the absence of a placebo control, and better prediction of those patients who can be expected to most benefit from treatment.

US 301 2 year cohort–baseline to year 2

Figure 1 US 301 two year cohort (baseline to year 2). Mean/median, interquartile ranges by tertiles of estimated yearly progression at baseline. LEF, leflunomide; MTX, methotrexate.

MN 302/4 2 year cohort–baseline to year 2
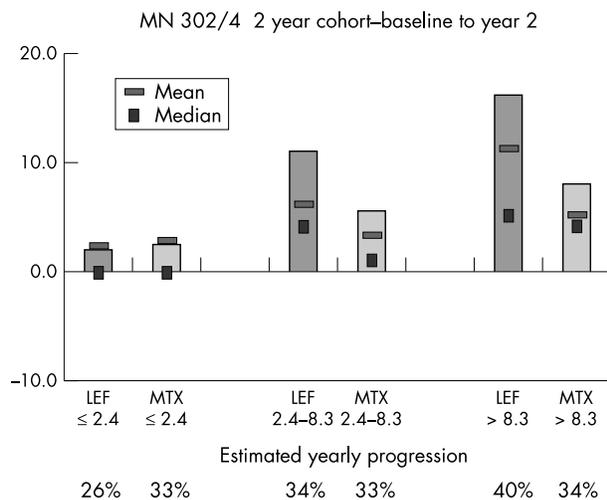
Figure 2 MN 302/4 two year cohort (baseline to year 2). Mean/median, interquartile ranges by tertiles of estimated yearly progression at baseline. Percentages represent the distribution of patients in each tertile in the year 2 cohort. LEF, leflunomide; MTX, methotrexate.

Results of the COBRA trial can be seen at www.annrheumdis.com

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