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Radiographic progression in clinical trials in rheumatoid arthritis: a systemic literature review of trials performed by industry

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ABSTRACT

Objectives To summarise radiographic data in randomised controlled trials (RCTs) as part of the radiographic inhibition claim of disease-modifying antirheumatic drugs (DMARDs) approved for patients with rheumatoid arthritis (RA).

Methods A systemic literature review was performed using the Medline database from 1994 to February 2020. The results were grouped based on the scoring methods (Sharp, Genant modification, van der Heijde modification) and RA patient populations.

Results One hundred sixty-eight publications were selected. After detailed assessment, 52 RCTs (7 methotrexate (MTX)-naive, 23 MTX inadequate response (IR), 9 DMARDs IR and 3 tumour necrosis factor-alpha inhibitors (TNFi) IR studies) were finally included. Information on patient population, scoring method used, reader reliability, statistical analyses and detailed radiographic data on baseline and change scores over multiple follow-up periods are presented.

Conclusion The data gathered in this review serve as a repository for the design of future trials with radiographic damage as an outcome.

Key messages

What is already known about this subject?

► Radiographic progression has been an important outcome assessment in rheumatoid arthritis randomised controlled trials (RCTs).

What does this study add?

► This is a systematic literature review of the available published information on demographic features, radiographic scoring methods, statistical analyses and detailed radiographic data.

How might this impact on clinical practice?

► This systematic literature review will help the design of RCTs with the radiographic inhibition claim of new drugs in the future.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterised by synovitis and destruction of synovial joints, leading to severe disability and premature mortality.[1] The introduction of disease-modifying antirheumatic drugs (DMARDs) in the treatment of patients with RA has led to improved management of RA, making not only (complete) symptom relief, but in addition the prevention of long-term structural damage the current goal of therapy.[2] The prevention of structural damage is also recognised by the Food and Drug Administration (FDA)[3] and the European Medicines Agency (EMA)[4] as a separate claim for a drug and defines the disease-modifying capability of a drug.

To date, radiographs are still considered the most appropriate method to assess structural damage in RA. MRI is regarded as a supportive imaging method but is not yet accepted as an alternative for radiographs by the FDA and EMA.[3 4] Validated radiographic scoring methods exist and are widely used for assessment and follow-up of joint damage in RA. Labelling for 'inhibition of radiographic progression' is granted to both synthetic and biological DMARDs (bDMARDs) based on randomised controlled trials (RCTs) in which retardation of structural progression is demonstrated using such validated scoring methods.

There is a general tendency for less radiographic progression in more recent RCTs.[5] This may be due to: earlier, more effective treatment of patients included in RCTs, leading to less structural damage at baseline[6]; or to less exposure to placebo (control) therapy due to earlier rescue. These developments have made it challenging to demonstrate the superiority of new drugs in inhibiting radiographic progression in RCTs. For future RCTs, this will require

even more careful selection of patients prone to radiographic progression and perhaps change in study design.[5] In this context, an overview of data used to get a label for 'inhibition of structural damage' by pharmaceutical companies would be of interest. Existing reviews of radiographic data do not include trials of more recent bDMARDs and targeted synthetic DMARDs (tsDMARDs), such as certolizumab, golimumab, tocilizumab and janus kinase inhibitors,[7] or do not consider methodological aspects of analysing radiographic data.[6]

The purpose of this overview was to summarise radiographic data in RCTs performed by pharmaceutical companies, usually to obtain the claim of radiographic inhibition, of all DMARDs approved for patients with RA. This can serve as a repository for the design including power calculations of future trials.

METHODS

This review is based on published articles reporting the results of RCTs for RA performed by pharmaceutical companies, in which the effects of new treatments on radiographic damage were evaluated. These trials were mostly used to obtain the registration as DMARDs for the respective treatment; however, some are pharmaceutical company-performed post-approval studies. A literature search on the topic was conducted in PubMed. The research question was translated into an epidemiological research question according to the PICO method (Patients, Intervention, Comparator and Outcome).[8] Patients were defined as adults with RA according to the 1987 American College of Rheumatology (ACR) criteria[9] or to the 2010 ACR criteria[10]; intervention was defined as any drug; comparator as placebo or another active drug; outcome was radiographic progression.

The literature search was carried out in PubMed. The database was searched using the following specific terms (synonyms and all possible combinations): rheumatoid arthritis, adalimumab, etanercept, infliximab, certolizumab, golimumab, anakinra, tocilizumab, rituximab, abatacept, tofacitinib, leflunomide, upadacitinib, baricitinib, peficitinib, ruxolitinib, filgotinib, ustekinumab, guselkumab, secukinumab, ixekizumab, canakinumab, brodalumab, sarilumab, secukinumab, sirukumab, radiographic, radiologic, structural or progression, Sharp, van der Heijde, Genant or Larsen. The search was limited to English language literature without a time limit. The last search was performed on February 6, 2020. The references of the selected articles were manually reviewed to identify additional relevant publications. Unpublished study enrolment dates were searched on ClinicalTrials.gov, fda.gov using, when available, the study identification number from publications. Pharmaceutical companies were also contacted to obtain unpublished data. Abstracts were not included as these contain insufficient detailed information.

The retrieved citations were managed using EndNote. One reviewer performed a selection based on titles and abstracts using predefined inclusion and exclusion criteria. The selected citations were discussed among two authors and included by consensus. To be included, articles had to contain data collected from any RCT performed by pharmaceutical companies for treatment registration (and their open-label extensions) or to further support the inhibition of radiographic progression, involving adult patients with RA (age >18 years). Articles with the following characteristics were excluded: investigator initiated and strategy studies, pediatric population, non-RA, languages other than English, no radiographic results reported, review articles, guidelines papers, case reports, commentary or letters. Based on this screening, full-text articles were obtained for more detailed reviewing.

Data extraction

An electronic form was used for the data extraction. The study characteristics including study design, patient enrolment dates, all relevant baseline demographics, clinical characteristics and all baseline and follow-up radiographic data were recorded. Trials were divided into methotrexate (MTX)-naïve, MTX inadequate responder (IR), DMARDs IR, or tumour necrosis factor-alpha inhibitors (TNFi) IR populations. The Larsen method was included in the literature search; however, this was used only in a limited number of older RCTs for which we have also results with the Sharp method. Therefore, we decided to exclude reporting data based on the Larsen method. A detailed data extraction flow chart is depicted in online supplementary figure 1.

RESULTS

A total of 1170 publications were identified in PubMed. Based on title and abstract review, 1002 publications were excluded because they did not include the population or intervention of interest, did not report radiographic results, were not randomised, controlled trials or were not performed by pharmaceutical companies. The remaining 168 publications were read full text. Of these, 104 manuscripts describing the results of 52 RA trials were included and were used for data extraction. A flow diagram summarising the screening and selection of articles is shown in figure 1.

The 52 included RCTs are presented in table 1. The MTX-naïve group included 17 RCTs (2 of a conventional synthetic DMARD (csDMARD) (leflunomide), 10 of a TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab) and 5 of a non-TNFi bDMARD or tsDMARD (abatacept, baricitinib, rituximab, tocilizumab, tofacitinib). MTX was mostly used as comparator. The MTX IR group included 23 RCTs (12 trials of TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab, biosimilar of etanercept, biosimilar of infliximab) and 11 of non-TNFi bDMARD or tsDMARD (anakinra, abatacept, baricitinib, denosumab, peficitinib, sarilumab, tocilizumab, tofacitinib, upadacitinib)) again with MTX

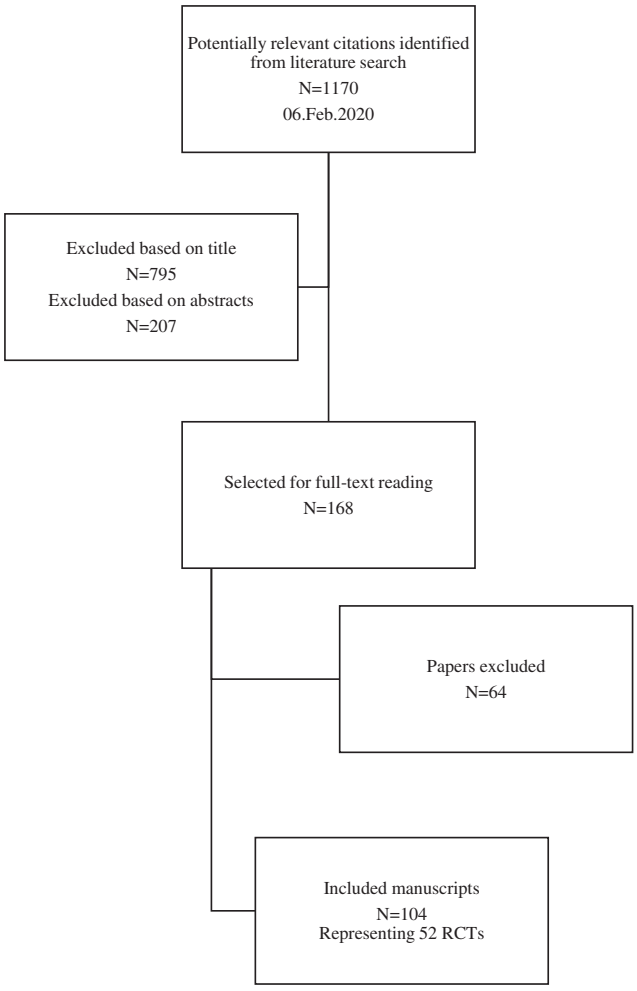

Figure 1 Flow chart of the trial selection process.

as the most frequently used comparator. MTX IR trials enrolled 77–651 patients in the comparator group and 85–651 patients in the treatment group. The DMARD IR group included 9 RCTs (1 csDMARD (leflunomide), 4 TNFi (certolizumab, etanercept, golimumab) and 4 non-TNFi bDMARDs and tsDMARDs (baricitinib, sirukumab, tocilizumab)), which included 91–556 patients in the comparator group and 102–557 patients in the treatment group. There were three trials conducted in a TNFi IR population investigating adalimumab, rituximab and secukinumab, which studied 16–214 patients in the comparator group and 17–308 patients in the treatment group.

Main patient characteristics at baseline

The main baseline demographic and clinical characteristics of the patients included in the 52 trials are reported in table 2. MTX-naïve trials generally included patients with short disease duration (mean duration per treatment group was less than a year), while MTX IR trials had a longer mean disease duration per treatment arm (1.7—11 years). Rheumatoid factor (RF) positivity was reported in 48 out of 52 trials (92.3%), and anti-citrullinated protein antibody (ACPA) positivity was described in 20 out of 52 trials (38.5%). In recent trials, the proportion of RF or ACPA positive patients increased (online supplementary figure 2). The majority of patients has high level of disease activity (table 2).

Scoring methodology

The description of the radiographic methodology used in each trial is shown in table 3. Conventional radiography (CR) of hands and feet was performed in all trials, except for IL-1Ra, where only hands were included. CRs were usually evaluated by two readers. However, several trials, such as leflunomide trials,[11] IL1-Ra,[27] PRIZE[22] and CAMEO[37] trial, only one reader scored CRs. When CRs were scored by two readers, the average score of the two readers was reported. The inter-reader and intra-reader intraclass correlation coefficients of status scores were reported in several RCTs and showed a high reliability of the measurements between readers and within a reader. The readers employed the Sharp method, the van der Heijde modification of the Sharp (SvdH) method or the Genant modification of the Sharp (GS) method. All methods include separate scores for erosions (ES) and joint space narrowing (JSN) that add to a total score. The maximum total score is 398 for the Sharp method, 448 for the SvdH and 290 for the GS method. Results were reported for the total score, as well as for the separate scores, per treatment arm. The change (Δ) in radiographic scores, which represents the difference between the scores at the follow-up visit and the scores at baseline, was the main outcome. A variety of approaches were used to deal with missing data, including linear extrapolation (LE), last observation carried forward and multiple imputation methods. For the patients who withdrew early or who received rescue medication, CR scores were usually estimated by LE of the scores from the radiographs taken at an early visit.

Radiographic results of the trials

Online supplementary table 1 presents the radiographic outcomes of all 52 trials until 1-year follow-up. The table is organised per scoring method (Genant, Sharp-van der Heijde and Sharp), and thereafter per patient population (MTX-naïve, MTX-IR, DMARD-IR, TNFi-IR). Per arm (intervention and control) the mean (SD), median (IQR) and range of the total score, erosion score and JSN score at baseline is presented. This is followed by the mean (SD) and median (IQR) change scores at 6 months and at 1 year. Finally, the percentage of non-progressors is presented. Non-progression in the RCTs is defined as: the number (%) of patients with ≤3 units of change in erosion scores at follow-up compared with baseline, the number (%) of patients with ≤0 units of change in total, erosion or JSN scores, the number (%) of patients with ≤0.5 units of change in scores, the number (%) of patients with ≤ smallest detectable difference (SDD), the number (%)

Table 1 Randomised controlled trials included for review

Patients population	Trial name	References	RA classfication criteria	ClinicalTrials.gov number	Enrollment start date*	Active drug	Comparator drug	Number of patients per treatment arm comparator-active†
MTX naïve	US301/ULTRA	[11]	1987	–	1995	LEF	PBO, MTX	118–182
	MN302‡	[11]	1987	–	1994	LEF	MTX	487–498
	ERA	[12]	1987	–	May 1997	ETN	MTX	217–208
	ASPIRE§	[13]	1987	–	July 2000	IFX	MTX	282–363
	PREMIER¶	[14]	1987	–	December 2000	ADA	MTX	257–274
	COMET‡	[15]	1987	NCT00195494	October 2004	ETN	MTX	263–265
	GO-BEFORE§, ¶	[16]	1987	NCT00264537	December 2005	GOL	MTX	160–159
	IMAGE	[17]	1987	NCT00299104	January 2006	RTX	MTX	249–250
	OPTIMA‡, **	[18]	1987	NCT00420927	December 2006	ADA	MTX	517–515
	AGREE‡,§	[19]	1987	NCT00122382	2005*	ABA	MTX	253–256
	HOPEFUL 1	[20]	1987	NCT00870467	March 2009	ADA	MTX	163–171
	FUNCTION	[21]	1987	NCT01007435	October 2009	TCZ	MTX	287–292
	PRIZE‡, **	[22]	1987	NCT00913458	October 2009	ETN	PBO, MTX	65–65
	ORAL Start	[23]	1987	NCT01039688	January 2010	TOF	MTX	186–397
	C-OPERA‡, **	[24]	2010	NCT01451203	October 2011	CZP	MTX	157–159
	C-EARLY‡, **, ††	[25]	2010	NCT01519791‡‡	January 2012	CZP	MTX	213–655
	RA-BEGIN§, ¶, ††	[26]	2010	NCT01711359	January 2013	BAR	MTX	210–215
MTX IR	European IL-1Ra§§	[27]	1987	–	–	ANA	PBO	116–121
	ATTRACT	[28]	1987	–	March 1997	IFX	MTX	88–87
	DE-O19	[29]	1987	–	February 2000	ADA	MTX	200–212
	AIM	[30]	1987	NTC00048568	November 2002	ABA	MTX	219–433
	LITHE‡, ¶¶	[31]	1987	NCT00106535	December 2004	TCZ	MTX	393–399
	RAPID 1	[32]	1987	NCT00152386	February 2005	CZP	MTX	199–393
	RAPID 2¶¶	[33]	1987	NCT00175877	June 2005	CZP	MTX	127–246
	GO-FORWARD	[34 35]	1987	NCT00264550	November 2005	GOL	MTX	133–133
	GO-FORTH	[36]	1987	NCT00727987	May 2008	GOL	MTX	88–87
	CAMEO**	[37]	1987	NCT00654368	June 2008	ETN	MTX	104–94
	J-RAPID¶¶	[38]	1987	NCT00791999	November 2008	CZP	MTX	77–85
	ACT-RAY‡, ¶, **	[39]	1987	NCT00810199	March 2009	TCZ	MTX	276–277
	ORAL-SCAN¶¶	[40]	1987	NCT00847613	March 2009	TOF	PBO	79–321
	GO-FURTHER	[41]	1987	NCT00973479	September 2009	GOL	MTX	197–395
	AMPLE***	[42]	1987	NCT00929864	October 2009	ABA	ADA	328–318
	DRIVE	[43]	1987	JapicCTI-101 263	August 2010	DNM	MTX	88–87

Continued

Table 1 Continued

Patients population	Trial name	References	RA classfication criteria	ClinicalTrials.gov number	Enrollment start date*	Active drug	Comparator drug	Number of patients per treatment arm comparator-active†
	PLANETRA†††	44	1987	NCT01217086	October 2010*	CPT13	IFX	304–302
	MOBILITY¶¶	45	1987	NCT01061736	March 2011	SAR	MTX	398–400
	RA-BEAM ***	46	2010	NCT01710358	November 2012	BAR	MTX	488–487
	SB4§§, †††	47	2010	NCT01895309	June 2013*	SB4	ETN	297–299
	SB2§§, †††	48	2010	NCT01936181	August 2013*	SB2	IFX	293–291
	RAJ4	49	2010	NCT02305849	July 2014*	PEF	MTX	170–175
	SELECT-COMPARE ***	50	2010	NCT02629159	December 2015*	UPA	MTX	651–651
DMARDs IR	MN301	11	1987	–	1994	LEF	PBO, SSZ	91–134
	TEMPO¶	51	1987	–	October 2000	ETN	MTX	228–231
	SAMURAI	52	1987	–	March 2003	TCZ	DMARDs	148–158
	GO-MONO	53	1987	–	May 2008	GOL	PBO	105–102
	HIKARI‡	54	1987	NCT00791921‡‡‡	November 2008	CZP	DMARDs§§§	114–116
	J-ETA§§	55	1987	–	–	ETN	MTX	176–192
	BREVACTA¶¶	56	1987	NCT01232569	March 2011	TCZ	DMARDs	219–437
	SURROUND-D	57	2010	NCT01604343	July 2012	SIR	DMRADs	556–557
	RA-BUILD	58	2010	NCT01721057	January 2013	BAR	DMARDs	228–229
TNFi IR	REFLEX	59	1987	NCT00468546	July 2003	RTX	MTX	209–308
	ADMIRE**	60	1987	NCT00808509	January 2009	ADA	MTX	16–17
	REASSURE	61	2010	NCT01377012	August 2011*	SEC	MTX	214–213

*If the patient's enrollment date could not be confirmed in the paper, it was replaced by the trial start date from the ClinicalTrials.Gov site.
†If the trial had multiple arms, the active drug group including the largest population of patients was marked as active in the table.
‡If the trial had multiple investigation periods/phases, the data for period/phase-1 or double-blind period data were only recorded.
§This trial permitted MTX user who had not received it more than 3 weekly.
¶This trial included a comparative study between monotherapy and combination therapy.
**This trial included a withdrawal or tapering study of active drug.
††DMARD-naïve patients were included.
‡‡This trial had two periods. In the case of withdrawal study period, the clinical trial number is NCT01521923.
§§This was not a trial name.
¶¶This trial included biological DMARDs user.
***This trial included a head to head study.
†††This was a non-inferiority trial of biosimilar drug.
‡‡‡This trial had two periods. In the case of open-label period, the clinical trial number is NCT00791921.
§§§DMARDs, other than MTX and leflunomide, were defined as comparator drugs.
ABA, abatacept; ADA, adalimumab; ANA, anakinra; BAR, baricitinib; CT-P13, biosimilar of infliximab; CZP, certolizumab; DNM, denosumab; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; GOL, golimumab; IFX, infliximab; IR, inadequate responder; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; PEF, peficitinib; RA, rheumatoid arthritis; RTX, rituximab; SAR, sarilumab; SB2, biosimilar of infliximab; SB4, biosimilar of etanercept; SEC, secukinumab; SIR, sirukumab; TCZ, tocilizumab; TNF, tumor necrosis factor; TOF, tofacitinib; UPA, upadacitinib.

Table 2 Baseline demographic and clinical characteristics of the patients*

Patients population	Trial name	Disease duration, years†	RF positivity, %	DMARDs failed, number, %	DMARD naïve, %	Taking steroids, %	CRP, mg/dL	ESR, mm/h	DAS28‡	SJC, number/ 66 joints§	HAQ DI	Total radiographic score
MTX naïve	US301/ ULTRA	6.5–7.0	59–65	0.8–0.9	40–45	53–55	1.9–2.5	33.8–38.4	-	13.0–14.8§	1.3	22.8–25.4
	MN302	3.7–3.8	74–76	1.1	33–34	45–49	4.1–4.2	51.0–51.6	-	15.8–16.5§	1.5	24.6–24.9
	ERA	1.0	87–89	0.5–0.6	54–61	39–42	3.3–4.4	-	-	24.0	-	11.2–12.9
	ASPIRE	0.8–0.9	71–73	0.0	65–68	37–39	2.6–3.0	43.0–45.0	6.6–6.8	21.0–22.0	1.5	11.2–11.6
	PREMIER	0.7–0.8	84–85	-	67–69	35–37	3.9–4.1	-	6.3–6.4	21.1–22.1	1.5–1.6	18.1–21.9
	COMET	0.7–0.8	67–70¶	-	22–76	49–50	3.6–3.7	47.8–49.3	6.5	17.1–17.6	1.6-.17	-
	GO-BEFORE	1.0–1.8	76–82	-	42–50	64–70	1.3–1.4	36.0–40.0	6.1–6.4	11.0–14.0	1.5–1.8	18.2–20.4
	IMAGE	0.9–1.0	85–87	-	69–72	44–48	3.0–3.4	-	7.0–7.1	20.0–22.4	1.7–1.8	6.9–7.7
	OPTIMA	4.0–4.5†	87–89	-	89–90	41–46	2.7–3.0	-	6.0C^{RP}	18.0	1.6	11.2–11.8
	AGREE	6.2–6.7†	96–97	-	96–97	49–51	3.1–3.6	-	6.2–6.3C^{RP}	21.9–22.9	1.7	6.7–7.5
	HOPEFUL 1	0.3	83–85	-	43–53	30–34	2.9–3.1	59.9–61.8	6.6	16.5–17.3	1.1–1.3	13.6
	FUNCTION	0.4–0.5	89–91	-	76–82	33–40	2.3–2.6	50.4–55.7	6.6–6.7	16.1–17.6	1.5–1.6	5.7–7.7
	PRIZE	2.9–3.5†	55–63	-	74–88	29–52	1.1–1.2	-	5.7–5.9	9.4–11.2	1.1–1.2	7.6–8.5
	ORAL Start	2.7–3.4	82–84	-	60–63	-	2.0–2.6	53.4–56.0	6.5–6.6	15.6–16.8	1.5	16.1–19.1
	C-OPERA	4.0–4.3†	93–96	-	81–82	16–20	1.3–1.5	38.4–43.7	5.4–5.5	8.3–8.4§	1.0–1.1	5.2–6.0
	C-EARLY	2.9†	97	0.0	100	30–34	1.1	42.0–44.0	6.7–6.8	12.4–13.0§	1.6–1.7	7.2–8.5
	RA-BEGIN	1.3–1.9	95–97	0.0	90–92	30–39	2.2–2.4	49.0–54.0	6.6	16.0	1.6–1.7	11.4–13.3
MTX IR	European IL-1Ra	3.7–4.3	69–71	-	19–34	41	4–4.2	46.8–53.2	-	25.6–26.6	1.5–1.6	24.7–29.6/ 12.0–16.6
	ATTRACT	9.0–12.0	77–84	2.5–2·8	-	54–65	3.3–4.2	49.0–52.0	-	21.0–24.0	1.7–1.8	66.6–81.9
	DE-O19	10.9–11.0	81–90	2.4	-	-	1.4–1.8	-	-	19.0–19.6	1.4	66.4–72.1
	AIM	8.5–8.9	79–82	-	88–91	69–72	2.8–3.3	-	6.4	22.1–21.4	1.7	44.5–44.9
	LITHE	9.0–9.4	81–83	1.6–1.7	22–19	62–70	2.1–2.3	45.9–46.5	6.5–6.6	16.6–17.3	1.5	28.5–28.7
	RAPID 1	6.1–6.2	80–84	1.3–1.4	-	-	1.4–1.6**	42.5–45.0**	6.9–7.0**	21.2.21.7	1.7	27.0–27.5
	RAPID 2	5.6–6.5	76–78	1.2–1.3	-	55–62	1.3–1.4	39.1–43.7	6.8–6.9	20.5–21.9	1.6	39.6–46.7
	GO-FORWARD	4.5–6.7**	81–87	-	-	65–75	0.8–1.0**	34.0–37.0**	5.9–6.1**	11.0–13.0**	1.3–1.4**	29.7–39.6**
	GO-FORTH	8.1–8.8	-	-	-	-	1.5–2.2	-	5.5–5.6	11.4–11.8	0.9–1.0	53.2–58.0
	CAMEO	9.0–9.3	61–68	1.0	-	74–78	1.2–1.3	21.8–23.0	5.4–5.4	9.7–10.3§	1.3–1.5	37.9–38.2
	J-RAPID	5.6–6.0	86–90	1.7–1.8	-	60–69	1.3–1.6	44.5–49.0	6.2–6.5	16.6–18.4	1.1–1.2	49.9–54.8
	ACT-RAY	8.2–8.3	-	1.9	-	49		-	6.3–6.4	14.4–15.3	1.5	30.4–37.1
	ORAL-SCAN	8.8–9.5	75–80	-	24–42	-	1.2–1.7	47.8–54.5	6.2–6.3	14.1–14.5	1.2–1.4	30.1–37.3
	GO-FURTHER	6.9–7.0	100.0††	-	0	-	2.2–2.8	-	5.9–6.0C^{RP}	14.8–15.0	1.6–1.6	47.6–50.3

Continued

Table 2 Continued

Patients population	Trial name	Disease duration, years†	RF positivity, %	DMARDs failed, number, %	DMARD naïve, %	Taking steroids, %	CRP, mg/dL	ESR, mm/h	DAS28‡	SJC, number/ 66 joints§	HAQ DI	Total radiographic score
	AMPLE	1.7–1.9	76–77	-	0	50–51	1.5–1.6	-	5.5C^{RP}	15.8–15.9	1.5	24.2–24.8
	DRIVE	2.2–2.3	67–69	-	74–82	42–45	0.5–0.8	-	3.6–4.0C^{RP}	8.9–10.5	0.3–0.5	10.0–13.6
	PLANETRA	1.7–1.9	72–75	-	0	-	1.9	46.6–48.5	5.8–5.9	15.2–16.2	1.6	68.3–64.8
	MOBILITY	8.6–9.5	83–87	-	0	63–67	2.0–2.4	-	5.9–6.0C^{RP}	16.6–16.8	1.6–1.7	46.3–54.7
	RA-BEAM	10.0	90–91	-	0	56–61	2.0–2.2	48.0–49.0	6.4–6.5	15.0–16.0	1.55–1.59	43.0–45.0
	SB4	6.0–6.2	78–79	-	0	-	1.3–1.5	46.4–46.5	6.5	15.0–15.4	1.49–1.51	38.9–43.3
	SB2	6.3–6.6	71–74	-	0	-	1.6–1.4	44.5–46.7	6.5	14.6–14.9	1.5	37.1–38.9
	RAJ4	4.3–4.4	-	-	0	-	2.5–2.6	51.0–53.8	5.8–6.1	6.8–7.0	0.91–1.05	25.0–28.4
	SELECT-COMPARE	8.0	87–88	-	0	60–62	1.8–2.0	-	6.4–6.5	16.0–17.0	1.6	34.0–36.0
	MN301	5.7–7.6	76–83	0.8–1.0	40–53	45–46	3.4–4.5	50.5–55.7	-	15.3–16.2§	1.7–1.9	41.9–46.3
DMARD IR	TEMPO	6.3–6.8	71–76	2.3	0	57–64	2.5–3.2	-	5.5–5.7	22.1–23.0	1.8	28.8–35.5
	SAMURAI	2.2–2.4	51	2.7–2.8	35	-	4.7–4.9	70.8–71.0	6.4–6.5	11.9–12.5	-	28.3–30.6
	GO-MONO	8.1–9.4	-		0	-	2.2–2.6	-	5.8–6.0	12.6–13.1	1.0–1.1	43.8–56.9
	HIKARI	5.4–5.8	85–89	1.8–1.9	0	66–71	1.6–1.7	49.0–51.0	6.1–6.3	13.8–15.5	1.1–1.2	36.5–46.1
	J-ETA	2.9–3.0	76–78	-	0	60–67	2.1–2.3	42.0–43.7	5.7–5.8	13.8–14.2	1.0–1.2	25.1–31.4
	BREVACTA	11.1–11.1	81–82	1.3–1.4	0	-	1.9–2.0	49.4–50.9	6.6–6.7	17.5–17.6	1.6–1.6	59.0–60.4
	SURROUND-D	8.3–8.8	78–80	-	0	59–65	2.4–2.5	-	-	-	1.5–1.6	41.8–42.5
	RA-BUILD	7.0–8.0	75–77	-	0	50–51	1.4–1.8	23.0–25.0	6.2–6.3	13.0–14.0	1.5–1.6	19.0–26.0
TNFi IR	REFLEX	11.7–12.1	79	2.4–2.6	0	61–65	3.7–3.8	48.0–48.4	6.8–6.9	22.9–23.4	1.9–1.8	47.9–48.3
	ADMIRE	7.6–10.4**	69–92	2.0	0	-	1.7–2.1**	-	2.1–1.7**	-	0.1–0.4**	22.5–42.5**
	REASSURE	7.8–9.0	91–94	-	0	58–62	-	-	5.6–5.7	16.4–17.2	1.7	48.1–57.7

*Values were expressed in mean unless otherwise indicated. The range of values was from the minimum to maximum, incorporating all study arms.
†If the disease duration was expressed as months, it is indicated.
‡DAS28 was based on the ESR.
§If the swollen-joints count was based on 28 joint examinations, it is indicated.
¶This value meant anti-citrullinated protein antibody positivity.
**Values were expressed in median.
††This trial included patients who was positive either in rheumatoid factor or anti-citrullinated protein antibody.
CRP, C reactive protein; DAS28, the 28-joint disease activity score; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index; IR, inadequate responder; MTX, methotrexate; RF, rheumatoid factor; SB2, biosimilar of infliximab; SB4, biosimilar of etanercept; SJC, swollen joints count; TNF, tumour necrosis factor.

Table 3 Radiographic methodology and statistical analysis in each trial

Patients population	Trial name	Scoring method	Interval radiographs*	Number of readers	Inter-/intra reader agreement	Assessment of agreement	SDC/SDD	Imputation methods			Sensitivity analysis
								LE	LOCF	Others	
MTX naïve	US301	Sharp	0, 1 year, (2 years)	1	0.972, 0.971†	-	-	No	No	-	Yes‡
	MN302	Sharp	0, 1 year, (2 years)	1	0.972, 0.971†	-	-	No	Yes	-	Yes‡
	ERA	Sharp	0, 6 months, 1 year, (2,4,5 years)	2 of 6	0.85/-	ICC	-	Yes	No	-	-
	ASPIRE	SvdH	0, 30 weeks, 1 year	2	-	-	SDD (0.93 at week 54)	Yes	No	Unconditional mean imputation§	-
	PREMIER	Sharp	0, 6 months, 1 year, (2, 5 years)	2 of 4	-	-	-	-	No	-	-
	COMET	SvdH	0, 1 year, 2 years	2	0.935/0.961	ICC	-	Yes	No	-	-
	GO-BEFORE	SvdH	0, 28 weeks, 1 year, (2, 5 years)	2	-/0.90	ICC	SDC (2.7 at week 52)	Yes	No	-	-
	IMAGE	Genant	0, 6 months, 1 year, (2 years)	2	-	-	-	Yes	No	-	Yes
	OPTIMA	SvdH	0, 26 weeks, 78 weeks	2	-	-	-	No	No	MI¶	-
	AGREE	Genant	0, 6 months, 1 year, (2 years)	-	-	-	-	Yes	No	-	Yes
	HOPEFUL 1	Sharp	0, 6 months	2	-	-	-	Yes	No	-	-
	FUNCTION	SvdH	0, 6 months, 1 year, (2 years)	-	-	-	-	Yes	No	-	Yes
	PRIZE	SvdH	0**, 39weeks**,65weeks**	1	-	-	-	No	Yes	-	-
	ORAL Start	SvdH	0, 6 months, 1 year, 2 years	2	-	-	-	Yes	No	-	Yes
	C-OPERA	SvdH	0, 6 months, 1 year	2	-	-	-	Yes	No	-	-
	C-EARLY	SvdH	0, 1 year	2	-	-	-	Yes	No	-	-
	RA-BEGIN	SvdH	0, 6 months, 1 year	2	-	-	SDC (1.15 at week 24, 1.41 at week 52)	Yes	No	-	Yes
MTX IR	IL-1RA	Genant	0, 6 months, 1 year	1	-	-	-	Yes	Yes	-	Yes‡
	ATTRACT	SvdH	0, 7 months, 1 year, (2 years)	2	0.89/-	ICC	-	No	No	CMI††	Yes
	DE-O19	Sharp	0, 6 months, 1 year, (3, 5 years)	2	-	-	-	Yes	Yes	-	Yes
	AIM	Genant	0, 1 year, (2 years, 5 years)	2	0.9/-	ICC	-	Yes	No	-	Yes
	LITHE	Genant	0, 6 months, 1 year, (2, 5yrears)	2	-	-	-	Yes	No	-	Yes
	RAPID 1	SvdH	0, 6 months, 1 year, (2 years)	2 of 3	-	-	-	Yes	Yes	-	Yes
	RAPID 2	SvdH	0, 6 months, (2 years, 3 years)	2	-	-	-	Yes	Yes	-	Yes

Continued

Table 3 Continued

Patients population	Trial name	Scoring method	Interval radiographs*	Number of readers	Inter-/intra reader agreement	Assessment of agreement	SDC/SDD	Imputation methods			Sensitivity analysis
								LE	LOCF	Others	
	GO-FORWARD	SvdH	0, 6 months, 1 year, (2 years)	2	-/0.95	ICC	SDC (1.8 at 52 week)	Yes	No	-	-
	GO-FORTH	SvdH	0, 6 months, (3 years)	2	0.98, 0.80‡‡	ICC	SDC (3.23 at 24 week)	No	No	-	-
	CAMEO	SvdH	0, 1 year, 2 years	1			-	No	Yes	-	Yes
	J-RAPID	SvdH	0, 6 months	2	-	-	-	Yes	No	-	-
	ACT-RAY	Genant	0, 6 months, 1 year, (2 years)	2	-	-	SDC (1.5 at 52 week)	No	Yes		-
	ORAL-SCAN	SvdH	0, 6 months, 1 year, 2 years	2	-	-	-	Yes	No	GEE, RCM	Yes
	GO-FURTHER	SvdH	0, 6 months, 1 year, (2 years)	2	0.76/0.97	ICC	SDC (1.91 at 52 week)	Yes	Yes	-	Yes
	AMPLE	SvdH	0, 1 year	2	-	ICC	SDC (2.8 at 52 week)	Yes	No	-	-
	DRIVE	SvdH	0, 6 months, 1 year	-	-	-	-	Yes	No	-	-
	PLANETRA	SvdH	0, 1 year	2	-	-	-	Yes	No	-	-
	MOBILITY	SvdH	0, 6 months, 1 year, (2 years)	2	-	-	-	Yes	Yes	-	Yes
	RA-BEAM	SvdH	0, 6 months, 1 year	2	-	-	SDC (1.22 at 24 week) (1.47 at 52 week)	Yes	Yes	MMRM	Yes
	SB4	SvdH	0, 1 year	2	-	-	SDC (2.3 at 52 week)	No	No	-	-
	SB2	SvdH	0, 1 year	2	-	-	-	No	No	-	-
	RAJ4	SvdH	0, 6 months, 1 year	2	-	-	-	Yes	No	-	Yes
	SELECT-COMPARE	SvdH	0, 3 months, 6 months	2	-	-	-	Yes	No	-	Yes
DMARD IR	MN301	Sharp	0, 6 months, 1 year, (2 years)	1	-	-	-	No	Yes	-	Yes‡
	TEMPO	SvdH	0, 6 months, 1 year, (2, 3 years)	2	0.85–0.98/0.90–0.99	ICC	SDD (6.2 at 52 week)	Yes	Yes	-	Yes‡
	SAMURAI	SvdH	0, 6 months, 1 year	2	0.96–0.98/0.99	ICC	-	Yes	No	-	-
	GO-MONO	SvdH	0, 6 months, (52, 104, 120 weeks)	2	0.98, 0.80/	ICC	-	No	No	Median change§§	-
	HIKARI	SvdH	0, 6 months, 1 year	2	-	-	-	Yes	No	-	-
	J-ETA	SvdH	0, 6 months, 1 year	2	-	-	SDD	Yes	No	-	-
	BREVACTA	SvdH	0, 6 months, 72 weeks	-	-	-	-	Yes	No	-	Yes
	SURROUND-D	SvdH	0, 18 weeks, 6 months, 1 year	-	-	-	-	Yes	No	-	-
	RA-BUILD	SvdH	0, 6 months	2	-	-	SDC (1.2 at 24 week)	Yes	Yes	-	-

Continued

Table 3 Continued

Patients population	Trial name	Scoring method	Interval radiographs*	Number of readers	Inter-/intra reader agreement	Assessment of agreement	SDC/SDD	Imputation methods			Sensitivity analysis
								LE	LOCF	Others	
TNFi IR	REFLEX	Genant	0, 6 months, 1 year, (2, 5 years)	2	-	-	-	Yes	No	-	Yes
	ADMIRE	SvdH	0, 28 weeks, 1 year	-	-	-	-	No	No	-	-
	REASSURE	SvdH	0, 1 year, (2 years)	-	-	-	-	No	No	MMRM	-

*Values in parentheses meant X-ray intervals during the long-term extension period.
†Values were correlation coefficients between the duplicate readings of baseline and year-1 radiographs when these were reread along with the year-2 films (correlation coefficient 0.971 for year-1 films and 0.972 for baseline films).
‡Sensitivity analysis was not performed in the primary analysis.
§Missing data was imputed using the change from baseline was estimated using the percentile of the entire patient population.
¶The Markov Chain Monte Carlo method was used to impute the missing radiographic data.
**Radiographs were obtained at baseline (1 year in the open-label phase), 39 weeks (91 weeks in the open-label phase) in the double-blind period.
††Missing data was imputed using group mean change.
‡‡ICC at baseline and week 24 was 0.98 and 0.80, respectively.
§§Changes from baseline in SvdH score for these patients were substituted with the median change for all patients.
CMI, Conditional mean imputation; DMARDs, disease-modifying antirheumatic drugs; GEE, generalised estimating equation; ICC, intra-class correlation coefficient; IR, inadequate responder; LE, linear extrapolation; LOCF, last observation carried forward method; MI, multiple imputation; MMRM, mixed model for repeated measures; RCM, Random coefficients model; SDC, smallest detectable change; SDD, smallest detectable difference; SvdH, van der Heijde modification of the Sharp score; TNF, tumour necrosis factor.

of patients with ≤ smallest detectable change (SDC). The SDD is defined as the smallest difference between two independent measurements (ie, patients) that can be interpreted as a 'real' difference beyond measurement error, while the SDC represents the SDC beyond measurement between two successive scores of the same patient.[62]

Of the 52 studies, 37 studies were analysed using the SvdH scoring method. From these, 8 were conducted in early RA (EA) patient populations and 29 were conducted in established patient populations. The baseline total SvdH score were 5–25 in EA trials and 9–79 in established RA trials (online supplementary figure 3). In both patient populations, no clear change in baseline total SvdH score was observed over the years.

Long-term extension (LTE) trials

There were 22 LTE trials as shown in online supplemen tary table 2. All trials have a follow-up of 2 years and several an additional follow-up up to 10 years in one trial.

Withdrawal or tapering trials

Finally, the data of the 7 trials that investigated radiographic progression after tapering or withdrawal are summarised in online supplementary table 3.

DISCUSSION

This is the first overview of radiographic data from all RCTs performed by pharmaceutical companies to obtain registration for new drugs that inhibit radiographic progression in RA or to further support their efficacy. As such this provides a rich source of information for planning future trials with radiographic damage as an outcome.

Fifty-two trials (7 trials used the GS method, 7 the Sharp method and 38 the SvdH method) conducted over 26 years have included a wide variety of RA patient populations. Over time, there has been no significant decline in the mean baseline radiographic score in the RCTs (online supplementary table 1 and figure 3). This result is different from the previous study by Rahman *et al*.[6] They described a dramatic decrease in severity of RA patients who participated in the TNFi trials. There are several possible explanations on this discrepancy. First, the previous study included only 5 trials in MTX-experienced population. It used to ATTRACT trial[28] conducted in 1999 as an anchor study that had the highest baseline radiographic score out of all the trials so far. If ATTRACT trial[28] is used as the reference point, the scatter plot is likely to show a negative slope. Second, the actual severity may have decreased, but the clinical trials have adapted the inclusion criteria to select patients with a high propensity for progression. For example, there is a trend that recent trials included more RF or ACPA positive patients. Some trials even required the presence of bone erosions as an inclusion criterion: among 17 trials conducted since 2010, 64.7% of the trials had the mandatory presence of erosions, as compared with 28.6% of

the studies prior to 2009. However, overall it is difficult to compare the true trend as data are obtained by different scoring methods and within the same scoring method by different readers. This may all result in variation of the scores, which may challenge the interpretation over time.

In clinical trials, missing values are inevitable. Because missing values can be a potential source of bias, various methods have been proposed to deal with this issue. LE has been the most widely used method in RA clinical trials. In this overview, 37 trials (71.2%), especially the older trials, employed LE methods. However, currently, the use of all available data in mixed models are the preferred method of analysis. For more detail, we refer to the literature.[63]

In conclusion, we summarised radiographic data from clinical trials used for the registration of drugs for the treatment of RA. This may serve as a repository for designing future clinical trials in RA with structural damage as an endpoint.

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