APPENDIX TO ARTHRITIS RHEUM 2010; 62; E-PUB AHEAD OF PRINT

Similar effects of disease modifying anti rheumatic drugs, glucocorticoids and biologics on radiographic progression in rheumatoid arthritis.

Meta-analysis of 70 randomised placebo or drug controlled studies including 112 comparisons

Niels Graudal MD, DrMedSci[1], Gesche Jürgens MD, PhD[2]

METHODS

Eligibility criteria

Rheumacon, a non-approved DMARD, was investigated in a single study and included in the control group, but no individual sub-meta-analysis of this drug was performed.

If a study contributed to several independent comparisons (i.e. with no intervention group in common) each of the independent comparisons could be included in one of the defined meta-analyses. Some studies contributed to two dependent comparisons with a common control group. These were included in the same meta-analysis splitting the shared control group into two groups with each half sample size to avoid double count of the control group (Main article:10).

Data collection process

Two investigators were contacted for supplementary information, which they could not provide, however.

SUPPLEMENTARY RESULTS (Tables A and B)

Supplementary meta-analyses

Group 1: Single DMARD vs. single DMARD (Table B, 1, I-V)

An additional analysis, which excluded the less effective DMARDs (chloroquine, per oral gold, azathioprine) and the rarely used D-penicillamine, which had no effect vs. placebo (Figure 1), and the non-approved rheumacon (54) from the comparisons, confirmed that none of the 5 most effective DMARDs (injectable gold, sulfasalazine, methotrexate, leflunomide and cyclosporine) were significantly superior, although injectable gold statistically was marginally inferior to the other 4 DMARDs ($p = 0.06$, Table B,1,I-V). The mean PARPR of these 5 DMARDs (29 study populations) was 0.92% (Table A). The mean PARPR of the 12 study populations of chloroquine, per oral gold, azathioprine and D-penicillamine was 1.96%.

Group 2, Single DMARD vs. placebo (Table B, 2, I-VII)

Less effective DMARDs: Cyclophosphamide was only investigated in one placebo-controlled study with no effect and was excluded from the analysis. The result of the meta-analysis of the 6 comparisons of chloroquine, D-penicillamine and per oral gold is shown in Table B,2,I.

In another sub analysis we excluded reference 58, which was the only study to investigate a mixture of DMARDS and which had an analogue control group (NSAID). The sub analysis of the 16 studies, which compare one DMARD with placebo, is shown in Table B, 2,II.

Sub analyses according to scoring method and estimation time show that the relative contributions to the effect sizes of studies scored with Sharp, Larsen or other methods and scored at different time points are similar (Table B, 2, III-VII).

Group 3: Combination of DMARDs vs. Single DMARD (Table B, 3, I-IV).

Sub analyses according to scoring method and estimation time show that the relative contributions to the effect sizes of studies scored with Sharp or Larsen, and scored at different time points only are marginally different (Table B, 3, I-IV).

Group 4: Glucocorticoids

Sub analyses according to scoring method and estimation time show that the relative contributions to the effect sizes of studies scored with Sharp, Larsen or other methods and scored at different time points are similar (Table B, 4, I-V).

Group 5: Biologic interventions: (Table B, 5, I-V)

I Anakinra vs. placebo (7):

The interleukin 1 receptor antagonist is the only biologic drug that has been tested as mono therapy against placebo. The results are shown in Appendix Table B, 5,I.

II Biologics vs. methotrexate (3;6;43;57):

This group contains one study of tocilizumab (43). The results are shown in Appendix Table B, 5,II.

III Biologic + methotrexate vs. biologic (6;57):

The results are shown in Appendix Table B, 5,III.

The results on methotrexate resistant and non-resistant are shown in Table B, 5, IV and V.

DISCUSSION

Within the last decade more new effective drugs for RA have appeared than during the previous century. We have therefore found it of relevance to give a complete survey of the known drugs and to evaluate the relative efficiencies. This is important especially because the new drugs are extremely more expensive than the old drugs, which therefore should be maximally exploited.

On the outcome level all evaluations were blind, but the use of different scoring methods could be a limitation. However, our supplementary analyses investigating the influence of the scoring systems on the effect estimates revealed no systematic differences between the scoring systems. The consistent use of mean values, initial full dose treatment and glucocorticoids in the biologic studies may exaggerate the effect estimate in the biologic studies compared with the non-biologic studies. On the other hand the lower frequency of dropping out and the more consistent use of the intention to treat principle in the biologic studies may have the opposite effect.

On the study level all studies were randomised, but the randomisation procedure insufficiently described in many studies (Appendix, Table A). Surprisingly fewer of the new biologic studies described allocation concealment than DMARD studies (Appendix, Table A), which relatively could overestimate the biologic effects.

In the analyses that we have presented as our main result we have excluded the small outlier studies that could indicate publication bias and consequently our main analyses are all symmetric in their funnel plots. Therefore publication bias should not influence these results.

Minor healing of erosions has been described in a minority of RA patients, but in practice joint destruction is the ultimate and irreversible outcome of RA summarizing the total of preceding disease (Main article: 4). A dissociation between joint destruction and inflammation may exist in some patients. Still, a slowing of the radiographic destruction generally reflects improvement in inflammatory variables such as joint swelling and ESR (Main article: 4;5).

Radiographic scores are skewed in their distribution and therefore better described by median and range than by mean and standard deviation. However in 90 of 112 comparisons a mean value was used to describe the radiographic score. The consequence is that the calculated progression rates are probably a little overestimated compared to what they would have been if medians were used. Therefore the use of medians would probably decrease the progression rates and the differences between them and thus further contribute to the conclusion that the differences between the different treatment principles are small.

Although the present approach to treatment (early, aggressive) is probably different from the one of the past, the difference between the older placebo- and DMARD controlled studies and the present biologic studies concerning disease duration and initial radiographic joint destruction were surprisingly small (Appendix, Table A). The duration of the combination DMARD studies were shorter (1.5 years) than the duration of the biologic studies (4.1 years). However in study that directly compared these two treatment principles (2,71) there was no difference in disease duration between these two groups and both treated groups were DMARD naive. Furthermore, the effects of biologics in the two DMARD naïve early RA biologic studies (1,2) were within the range of the other biologic studies (Figure 4). This indicates that similar effect sizes in groups 3 and 5 cannot be attributed to the different periods of investigation, differences in disease duration or differences in DMARD naivety.

Indeed, the relative effect was larger in patients treated with biologics + methotrexate than in patients treated with 2 DMARDs (80% vs. 50%), but in all biologic studies initial full dose biologic treatment was used whereas 14 of 17 DMARD combination studies were step-up studies. Thus the later attainment of full-dose in the combination DMARD studies would delay the effect on joint destruction. On the other hand the inclusion of DMARD resistant patients in the biologic studies could be a bias in the opposite direction. However the sensitivity analysis of the biologic studies including DMARD resistant patients versus non-resistant patients indicated that biologics were insensitive to previous DMARD resistance.

Table A: Baseline- and study course characteristics in the 5 intervention groups

	Group 1 DMARD vs. DMARD	**Group 2** DMARD vs. Placebo	**Group 3** DMARD Combination	**Group 4** Glucocor-ticoids	**Group 5** Biologics
1 Baseline Characteristics					
Number of studies	20	15	15	13	15
Number of comparisons	41	17	17	14	23
Allocation concealment (n/all)	23/41	10/17	11/17	11/14	5/23
Sequence generation (n/all)	14/41	9/17	9/17	9/14	10/23
Double blind comparisons (n/all)	23/41	15/17	8/17	9/14	17/23
Radiograph reader blinded (n/all)	41/41	17/17	17/17	14/14	23/23
Scoring system (Sharp/Larsen/Other)	17/20/4	7/6/4	9/8/0	6/5/3	20/3/0
R-score reported as Mean/Median (n/n)	32/9	14/3	10/7	11/3	23/0
Number of patients (active/control)	3315/3637	964/577	948/1019	883/867	3846/2790
Mean disease duration in years, median (range)	3.8 (0.5-8.5)	3.2 (0.5-11.1)	1.5 (0.3-6.3)	2.6 (0.3-14.5)	4.1 (0.5-11.8)
Initial R-score (% of max)	11.8 (0.3-33.8)	10.1(0.4-28.7)	5.5 (0.3-16.6)	5.0 (0.7-18.8)	7.2 (0.7-23.1)
Radiographic estimation time (months)	12 (6-60)	12 (6-24)	12 (6-24)	12 (12-24)	12 (6-12)
2 Study Course Characteristics					
Drop-out (% of participants, active/control)	28/28	32/33	21/29	22/24	10/13
Due to lack of response	10/10	11/33	5/10	6/6	7/17
Serious side effects (% of participants, active/control)	19/19	16/7	14/13	10/11	8/7
Treatment persistence (% of participants, active/control)	63/63	66/54	82/75	84/78	84/71
Use of per oral glucocorticoids (Number of studies, yes/no)	32/9	11/6	10/7	14/0	21/2
Use of per oral glucocorticoids (% of participants, active/control)	35/35	38/55	51/40	100/0	43/43
Dose of per oral glucocorticoids (Median, mg)	<10mg	<10mg	<10mg	<10mg	<10mg
PARPR in DMARD mono group (%)	0.92	0.48	1.60	1.05	0.78
Change in treatment strategy (Number of studies, yes/no)	14/27	3/14	7/10	10/4	7/16
Intention to treat/Completer (n/n)	19/22	8/9	11/6	11/3	20/3
Step-up therapy/ Initial full dose therapy (n/n)	26/15	3/14	14/3	0/14	0/23

Table B: Primary outcome of treatment vs. control in rheumatoid arthritis: Results of supplementary meta-analyses of the effect on the difference in the percentage of the annual radiographic progression rate (PARPR).

Treatment	N, Comparisons	n, participants	Model	PARPR (PA) % mean difference (95% CI)	Z	P-value	Control PA, (%) (C)	Relative effect % (PA)/C
1 Effective (E) Single DMARD (D) vs. Effective Single DMARD								
I Leflunomide vs D	3	1173	Fixed	-0.06 [-0.33, 0.20]	0.47	0.63		
II Methotrexate vs D	9	1754	Fixed	-0.08 [-0.32, 0.16]	0.63	0.53		
III Sulfasalazine vs D	3	418	Fixed	-0.07 [-0.40, 0.26]	0.41	0.68		
IV Injectable gold vs D	3	681	Fixed	0.34 [-0.01, 0.69]	1.89	0.06		
V Cyclosporine vs D	3	464	Fixed	0.10 [-0.78, 0.99]	0.23	0.82		
2 Single DMARD vs. Placebo (P)								
I Less effective D vs. P	6	488	Random	-1.04 [-2.76, 0.68]	1.18	0.24	4.28	-24
II D vs. P (-ref 66)	16	1370	Random	-1.47 [-2.26, -0.58]	3.63	0.0003	2.81	-52
III Larsen scoring	6	506	Random	-1.51 [-2.66, -0.35]	2.55	0.01	2.51	-60
IV Sharp scoring	6	555	Fixed	-0.73 [-1.14, -0.31]	3.45	0.0006	1.27	-57
V Other scorings	4	309	Random	-3.38 [-5.23, -1.52]	3.56	0.0004	5.45	-62
VI ET*,12 months	12	1124	Random	-1.38 [-2.46, -0.31]	2.53	0.01	3.22	-43
VII ET, 6 or 24 months	5	417	Fixed	-1.21 [-1.73, -0.68]	4.52	0.0001	2.09	-58
3 Combination of DMARDs vs. Single DMARD								
I Larsen scoring	8	935	Random	-1.46 [-1.99, -0.93]	5.44	0.0001	2.37	-62
II Sharp scoring	9	1032	Random	-0.45 [-0.82, -0.08]	2.4	0.02	0.85	-53
III ET, 12 months	11	1191	Random	-0.66 [-1.10, -0.21]	2.89	0.004	1.34	-49
IV ET, 6,18 or 24 months	6	776	Random	-1.26 [-1.85, -0.67]	4.18	0.0001	1.81	-70
4 Glucocorticoid +/- DMARD vs. placebo: +/- DMARD								
I Larsen scoring	5	713	Fixed	-0.51 [-0.81, -0.21]	3.3	0.001	1.24	-41
II Sharp scoring	6	843	Random	-0.73 [-1.21, -0.25]	3.0	0.003	1.53	-48
III Other scorings	3	194	Random	-1.68 [-4.96, 1.61]	1.0	0.32	3.52	-48
IV ET, 12 months	11	1231	Random	-0.86 [-1.28, -0.43]	3.95	0.0001	1.63	-53
V ET, 24 months	3	519	Fixed	-0.21 [-0.36, -0.06]	2.76	0.006	0.44	-48
5 Biologic (B) +/- Mtx vs. Mtx/Biologic								
I Anakinra vs Placebo	3	364	Fixed	-3.49 [-6.76, -0.21]	2.08	0.04	8.67	-40
II B vs Mtx	4	1453	Random	-0.51 [-0.76, -0.27]	4.11	0.0001	0.87	-59
III B.+.Mtx vs. B	2	800	Fixed	-0.33 [-0.44, -0.23]	6.33	0.0001	0.54	-62
IV B+Mtx vs. Mtx, NR**	6	2499	Fixed	-0.66 [-0.81, -0.52]	9.06	0.0001	0.82	-80
V B+Mtx vs. Mtx, R***	6	2466	Fixed	-0.59 [-0.73, -0.43]	7.29	0.0001	0,72	-82

*ET: Estimation time; **NR: Non-resistant for methotrexate; ***R: Resistant for methotrexate

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