Editorial

Results from Controlled Clinical Trials: How Relevant for Clinical Practice?

About 12 years ago *The Journal* published Hawley and Wolfe's study of 122 controlled clinical trials and observational studies of disease modifying therapies in rheumatoid arthritis (RA). The authors' conclusion was that observational studies following controlled clinical trials can give important information about effectiveness of RA therapies not available from controlled trials alone[1]. In an accompanying editorial, Felson, after discussing the benefits and drawbacks of the 2 trial designs, concluded that observational studies from clinical practice and randomized controlled trials (RCT) have complementary roles in providing information about the therapy in RA[2].

One of the major criticisms against RCT is related to the selection of patients. Inclusion criteria are frequently very strict, raising questions about the external validity of the results[3]. In this issue, Sokka and Pincus report an examination of the proportion of patients that have disease activity scores exceeding levels usually used as inclusion criteria of RCT of disease modifying therapies[4]. In the cohort with established disease, who had been under routine specialized care for an average of 6 years, only 19.9% of the patients had both 6 or more swollen and tender joints, 25% had erythrocyte sedimentation rate (ESR) of 28 mm/h or more, and 45.9% had morning stiffness of 45 minutes or more. Few of these patients were in remission, and all were taking a disease modifying antirheumatic drug (DMARD). Sokka and Pincus conclude that the majority of patients seen in routine care did not meet criteria for inclusion in most contemporary RA clinical trials. Further, they conclude that controlled trial data are not available concerning results of treatment with the new biological agents or DMARD in a large proportion, if not a majority, of patients with RA at present[4].

It may be argued that their data were collected at a time when the patients were using DMARD and that the data do not reflect the disease status when therapy was initiated. To provide complementary information we have therefore analyzed the disease activity status according to the same "rules" in a cohort of 1440 patients with inflammatory arthropathies at the time when DMARD therapy was started. Morning stiffness was not evaluated and for this reason could not be included in the calculations. These patients were enrolled during the last 2 years from 3 rheumatology departments into a registry of consecutive starters of DMARD regimens. Indications for starting biological agents were in accord with published recommendations for the use of such agents[5].

More than 20 different monotherapy or combination regimens were used, and they were grouped into the following 6 categories: monotherapy or combination regimens with etanercept or infliximab (n = 171, 11.9%), monotherapy with leflunomide (n = 196, 13.6%), methotrexate (n = 549, 38.1%), sulfasalazine (n = 221, 15.3%), other monotherapies (n = 173, 11.8%), and other DMARD combinations (n = 130, 9.0%). As shown in Table 1 patients starting with a regimen with a tumor necrosis factor (TNF) blocking agent had the most active and severe disease, whereas patients starting with sulfasalzine monotherapy had the mildest disease. Table 2 shows that 59.5% of the patients starting with TNF-blocking agents had both 6 or more swollen and tender joints, 59.8% had ESR exceeding 28 mm, and 36.9% fulfilled all 3 disease activity criteria. Lower percentages of patients fulfilled these disease activity criteria in regimens with the established DMARD (Table 2). Thus, our data support that at least two-thirds of the patients starting with biological agents in clinical practice have lower disease activity than the levels usually required to be enrolled in controlled clinical trials, and that this proportion is much higher for patients starting with methotrexate and sulfasalazine (Table 2). If other inclusion and exclusion criteria are taken into account, we assume that less than 10% of the patients starting with biological agents would fulfill the inclusion and exclusion criteria conventionally used in clinical trials of such agents.

Thus, Sokka and Pincus correctly raise the question

See Most patients receiving routine care for RA in 2001 did not meet inclusion criteria for most recent clinical trials or ACR criteria for remission, *page 1138*.

Table 1. Level of disease activity and severity across 6 treatment groups in a practice based longitudinal observational study of DMARD regimens. Values are mean for continuous variables and percentage of patients for counts.

	TNF (n = 171)	LEF (n = 196)	MTX (n = 549)	SSZ (n = 221)	MONO (n = 173)	COMBO (n = 130)
28 SJC	9.7	8.4	7.6	4.8	6.7	8.4
28 TJC	10.7	8.1	7.4	5.3	7.0	8.7
ESR, mm/h	38.4	33.2	29.3	26.4	29.6	30.9
CRP, mg/l	36.7	28.0	24.9	20.6	24.8	27.0
DAS	5.75	5.22	4.91	4.30	4.74	5.20
Pain VAS, mm	60.8	52.8	49.5	46.0	47.8	49.7
Patient global VAS, mm	64.1	55.5	52.2	48.5	50.3	57.0
Investigator global VAS	56.9	47.7	42.9	35.6	38.4	47.4
MHAQ (score 1–4)	2.01	1.88	1.71	1.60	1.76	1.76
No. of previous DMARD	4.30	3.49	1.22	0.73	2.56	1.88
Rheumatoid factor, %	63.0	67.2	41.0	28.9	52.7	52.8
Erosive disease, %	79.1	74.9	41.8	32.5	47.3	53.6

28 SJC: 28 swollen joint count; 28 TJC: 28 tender joint count; DAS: Disease Activity Score; VAS: visual analog scale; MHAQ: Modified Health Assessment Questionnaire; DMARD: disease modifying antirheumatic drugs; TNF: TNF-blocking agents; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; MONO: other monotherapy regimens; COMBO: other combination regimens.

Table 2. Proportions of patients with disease activity exceeding levels commonly used in protocols for controlled drugs trials of DMARD.

	TNF (n = 171)	LEF (n = 196)	MTX (n = 549)	SSZ (n = 221)	MONO (n = 173)	COMBO (n = 130)
28 SJC ≥ 6	67.6	65.3	53.5	35.0	51.4	65.9
28 TJC ≥ 6	68.5	60.0	52.1	36.5	45.3	60.5
ESR ≥ 28 mm/h	59.8	47.9	40.7	35.0	41.3	44.1
CRP ≥ 20 mg/l	60.6	48.7	41.4	32.7	37.6	46.0
28 SJC ≥ 6 and 28 TJC ≥ 6	59.5	49.7	38.5	22.8	34.3	52.7
28 SJC ≥ 6, 28 TJC ≥ 6 and ESR ≥ 28	36.9	22.1	17.8	11.9	20.3	25.6

28 SJC: 28 swollen joint count; 28 TJC: 28 tender joint count; TNF: TNF-blocking agents; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; MONO: other monotherapy regimens; COMBO: other combination regimens.

whether the inclusion criteria used in clinical trials are appropriate[4]. The data presented by them and the above data clearly show that inclusion criteria could be reconsidered regarding levels of disease activity.

An additional concern regarding inclusion criteria relates to the classification of RA, especially in trials of patients with recent onset. It has been established that RA should be treated early, because a delay in therapy may lead to less favorable treatment results[6-8]. One problem with early diagnosis in RA is that some items of the classification criteria reflect disease activity and others reflect disease severity[9]. It may take some time before some items are fulfilled, especially rheumatoid factor, erosive disease, and rheumatic nodules[10]. It has also been shown that RA only constitutes a proportion of all patients with inflammatory arthropathies, and that the proportion classified as undifferentiated polyarthritis is of the same magnitude as RA[11,12]. Followup studies of patients with early arthritis, including both RA and arthritides not classified as RA, indicate that disease severity variables should be considered more than the exact diagnosis when considering DMARD therapy[13,14]. Such an approach could also be used in protocols for controlled clinical trials of DMARD, especially if patients with short disease duration are to be enrolled.

In summary, it is timely now to reconsider traditional inclusion and exclusion criteria of protocols for DMARD RCT, in particular with respect to how they can produce better results of relevance for clinical practice. We have focused on 2 aspects — the level of disease activity and the classification criteria. However, stringent inclusion and exclusion criteria are also required in RCT. Therefore, we will still also need longitudinal observational studies, with data reflecting real life[1,2,15].

RCT and observational studies provide information that is complementary. Results from some clinical databases of DMARD regimens and biological agents have indicated that this is also true for the newer drugs[16,17] and that such databases have the potential to provide information of major importance for clinicians, payers, and pharmaceutical companies alike.

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