Review

Randomized controlled trial design in rheumatoid arthritis: the past decade

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Abstract

Much progress has occurred over the past decade in rheumatoid arthritis trial design. Recognized challenges have led to the establishment of a clear regulatory pathway to demonstrate efficacy of a new therapeutic. The use of pure placebo beyond 12 to 16 weeks has been demonstrated to be unethical and thus background therapy and/or early rescue has become regular practice. Goals of remission and 'treating to targets' may prove more relevant to identify real-world use of new and existing therapeutics. Identification of rare adverse events associated with new therapies has resulted in intensive safety evaluation during randomized controlled trials and emphasis on postmarketing surveillance and use of registries.

Introduction

Much has changed since methotrexate was approved for treatment of active rheumatoid arthritis (RA) in 1986 based on a total of 126 patients enrolled in two randomized controlled trials (RCTs) [1,2] and treated for a maximum of 24 weeks. Today, RCTs are expected to be 6 to 24 months in duration and employ composite outcomes by American College of Rheumatology (ACR) responses and/or Disease Activity Score (DAS), inhibition of radiographic progression at 6 and 12 months with continued benefit at 24 months, and improvement in physical function and health-related quality of life at 6 months with continued benefit over long-term treatment. Over the past decade, approval of etanercept [3,4] and leflunomide [5] in 1998 and infliximab in 1999 [6] established a firm regulatory precedent in RA, resulting in the introduction of three more disease-modifying antirheumatic drug (DMARD) therapies (Figure 1) with another three expected within the year.

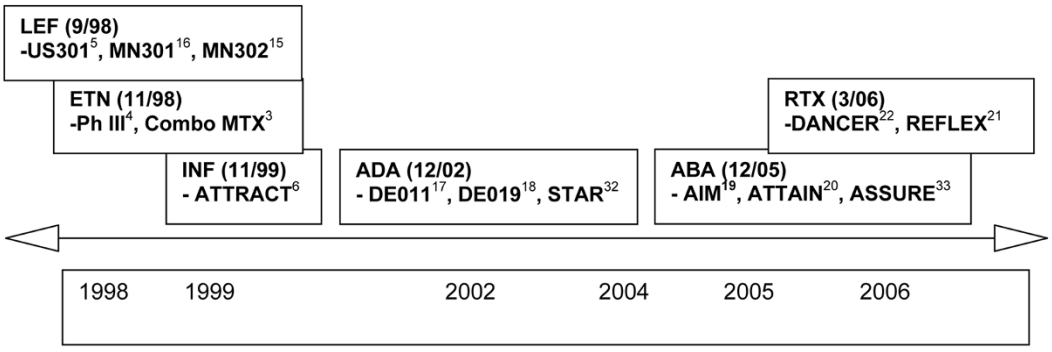
This progress in clinical development was driven, in part, by the *Guidance Document for Development of New Therapies for Treatment of RA*, which was issued by the US Food and Drug Administration (FDA) and finalized in 1998 [7], followed by recommendations from the European Agency for the Evaluation of Medicinal Products in 2004 [8]. Together, these documents set a precedent for requiring longer-term RCTs, of 12 to 24 months in duration, evaluating radiographic progression and patient-reported physical function in addition to accepted outcomes assessing signs and symptoms of disease.

This review will address difficulties in comparing clinical trials, including the importance of comparator groups, background therapy, and means to use placebo controls. Additionally, identification of rare adverse events in RCTs and confirmed in postmarketing surveillance as well as newer approaches designed to reflect clinical practice more realistically will be discussed.

The tremendous progress in clinical development in RA over the past decade has revolutionized rheumatology and significantly benefited our patients. It is hoped that this precedent will lead to similar advances in other rheumatologic diseases, although to date these remain more elusive. Hopefully, the next decade will bring new agents to address the large unmet needs in other rheumatic diseases.

ACR = American College of Rheumatology; ACR20 = American College of Rheumatology 20% improvement criteria; AMBITION = Actemra versus Methotrexate Double-Blind Investigative Trial in Monotherapy; ASPIRE = Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; ASSURE = Abatacept Study of Safety in Use with Other Rheumatoid Arthritis Therapies; ATTRACT = Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy; COX-2 = cyclooxygenase-2; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; ERA = Etanercept in Early Rheumatoid Arthritis; FDA = US Food and Drug Administration; HAQ-DI = Health Assessment Questionnaire-Disability Index; JIA = juvenile inflammatory arthritis; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; RCT = randomized controlled trial; STAR = Safety Trial of Adalimumab in Rheumatoid Arthritis; TEMPO = Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; TNF-I = tumor necrosis factor inhibitor; TSS = Total Sharp/Sharp van der Heijde score.

Figure 1



Timeline of regulatory (US Food and Drug Administration) approvals for currently used disease-modifying antirheumatic drugs over the past 10 years. Major regulatory trials used in approval of each agent are listed below the agent. For reference, methotrexate was approved in 1985, cyclosporine in 1995. ABA, abatacept; ADA, adalimumab; AIM, Abatacept in Inadequate Responders to Methotrexate; ASSURE, Abatacept Study of Safety in Use with Other Rheumatoid Arthritis Therapies; ATTAIN, Abatacept Trial in Treatment of Anti-Tumor Necrosis Factor Inadequate Responders; ATTRACT, Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy; DANCER, Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis; ETN, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; REFLEX, Randomized Evaluation of Long-Term Efficacy of Rituximab; RTX, rituximab; STAR, Safety Trial of Adalimumab in Rheumatoid Arthritis.

Difficulties in comparing trial data: no two randomized controlled trials are the same

There have been few head-to-head trials of biologic agents in RA. It is not surprising that sponsors of regulatory trials have not pursued this study design, leaving clinicians only the option of comparing data across RCTs. To do so requires trials that enroll patient populations with similar demographics and disease characteristics and that use comparable treatment interventions and outcome measures – a tall order, especially in heterogeneous diseases such as RA (Table 1).

Across trials, it is clear that therapeutic responses are not consistent. This is perhaps best exemplified by the variability of ACR20/50 (ACR 20%/50% improvement criteria) responses with methotrexate, which range from 46% to 78% at 1 year and from 56% to 84% at 2 years (Table 2). These cannot be completely explained by differences in median methotrexate doses, use of folic acid supplementation [9], or enrollment of subjects with early versus well-established disease. Even in patients with early disease (duration of less than or equal to 1 year), ACR20/50 responses with methotrexate monotherapy ranged from 54%/32% (ASPIRE [Active Controlled Study of Patients Receiving Infliximab for Treatment of RA of Early Onset]) [10] to 63%/46% (PREMIER) [11] to 65%/42% (Etancercept in Early RA [ERA]) [12]. Similarly, in three-arm RCTs comparing either monotherapy with combination tumor necrosis factor inhibitor (TNF-I) + methotrexate, ACR20 responses for TNF-I monotherapy versus combination varied from 32% versus 50% (ASPIRE) and 41% versus 62% (PREMIER) in early disease to 48% versus 69% in a population with approximately 7 years of disease duration (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes [TEMPO]) [13]. Those naïve to methotrexate (ASPIRE and PREMIER) as well as those receiving successful therapy for not more than 6 months generally will have more favorable responses to this 'gold standard' DMARD.

Radiographic progression is also quite variable across protocol populations receiving methotrexate, ranging from 0.9 to 2.8 Total Sharp/Sharp van der Heijde score (TSS) points (range 0 to 448) at 12 months in populations with 6 to 7 years of disease duration (US301 and TEMPO) [5,13] to 1.3 to 5.7 TSS points in early disease trials (ERA, ASPIRE, and PREMIER) [10-12] (Figure 2). Differences in progression rates are best predicted by pre-existing damage (for example, TSS at baseline). Calculating estimated yearly progression (baseline TSS divided by mean disease duration) illustrates the broad differences in expected progression rates across protocols, ranging from 3.5 to 6.6 in established disease (US301 and TEMPO) to 8.4, 9.5, and 27.4 (ERA, ASPIRE, and PREMIER) in early disease (Figure 2). It is therefore important to interpret RCT data carefully in the context of demographic and baseline disease characteristics of each population, realizing that no two trials have enrolled truly similar populations, even with similar designs.

Active controlled trials

An active controlled trial demonstrating 'noninferiority' of a new to an accepted therapy is a standard design to demonstrate efficacy and may avoid use of placebo. As a consequence of the variability in responses discussed above, it is a challenge to predict clinical outcomes in protocols and accurately calculate sample sizes, particularly when using an active comparator, even the gold standard methotrexate. This has prompted the FDA and the European Medicines Agency

Table 1

Randomized controlled trials of disease-modifying antirheumatic drugs approved since 1998 that have supported regulatory labeling

Trial	Year published	Study drug	Mean disease duration at BL	Prior therapy	Duration
US 301 [5]	1999	LEF vs. MTX vs. PL	7.0 (± 8.6)	MTX-naïve	2 years
MN 301 [16]	1999	LEF vs. SSZ vs. PL	7.8 (± 8.6)	SSZ-naïve	6 months + continuation
ETN Phase 3 [4]	1999	ETN vs. PL	12[a]	DMARD failures	6 months
ETN+MTX [3]	1999	ETN+MTX vs. PL+MTX	13[a]	MTX >6 months	6 months (primary at 3)
ATTRACT [6]	1999	INF+MTX vs. MTX+PL	8.4 (± 7.7)	MTX >3 months	2 years
MN 302 [15]	2000	LEF vs. MTX	3.7 (± 3.2)	MTX-naïve	1 year + continuation
ERA [12]	2000	ETN vs. MTX	0.9 (± 0.8)	MTX-naïve	2 years
TEMPO [13]	2004	ETN vs. MTX vs. ETN+MTX	6.8 (± 5.5)	TNF-naïve	2 years
ASPIRE [10]	2004	INF vs. MTX vs. INF+MTX	0.9 (± 0.8)	MTX-naïve	1 year
PREMIER [11]	2006	ADA vs. MTX vs. ADA+MTX	0.7 (± 0.8)	MTX-naïve	2 years
ATTAIN [20]	2005	ABA+MTX vs. MTX+PL	12.0 (± 8.5)	MTX >3 months, TNF-I failure	6 months + continuation
AIM [19]	2006	ABA+MTX vs. MTX+PL	8.5 (± 7.3)	MTX >3 months, TNF-I-naïve	6 months + continuation
REFLEX [21]	2006	RTX+MTX vs. MTX+PL	11.7 (± 7.7)	MTX >3 months, TNF-I failure	6 months + continuation
DANCER [22]	2006	RTX+MTX vs. MTX+PL	10.5[a]	MTX >3 months, TNF-I-naïve	6 months + continuation

The table notes mean duration of disease at baseline, background, and/or failed disease-modifying antirheumatic drug (DMARD) therapy at entry and length of study. [a]Standard deviation not reported. ABA, abatacept; ADA, adalimumab; AIM, Abatacept in Inadequate Responders to Methotrexate; ATTAIN, Abatacept Trial in Treatment of Anti-Tumor Necrosis Factor Inadequate Responders; BL, baseline; DANCER, Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis; ETN, etanercept; INF, infliximab; LEF, leflunomide; MTX, methotrexate; PL, placebo; REFLEX, Randomized Evaluation of Long-Term Efficacy of Rituximab; RTX, rituximab; SSZ, sulfasalazine; TNF=I, tumor necrosis factor inhibitor.

Table 2

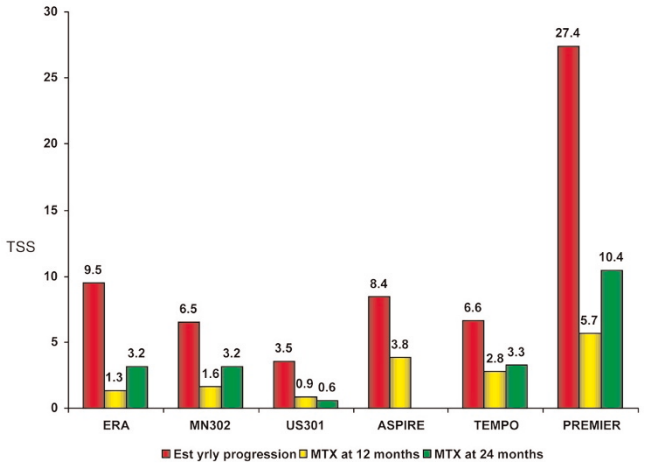
Therapeutic responses to methotrexate

			ACR ≥20 responses at	
Study/Trial	Mean disease duration	Median MTX dose (mg/week)	12 months	24 months
Haagsma, *et al*. [74]	3 months	10	71%	NR
Möttönen, *et al*. [57]	8 months	10	78%	84%
ERA [12,75]	11 months	18[a]	65%	59%
MN 302 [15]	3.8 years	10	65%[b]	72%
US 301 [5]	6.5 years	15[a]	46%[b]	67%
ASPIRE [10]	7 months	19[a]	54%[b]	NR
TEMPO [13]	6.6 years	17[a]	75%	71%
PREMIER [11]	8 to 9 months	16[a]	63%[b]	56%

Therapeutic responses to methotrexate (MTX) are not consistent across trials and cannot be explained solely by differences in duration of disease or median MTX dose. [a]With regular folate supplementation. [b]Designated 12 month outcomes were analyzed with an intention to treat (ITT) analysis with non-responder imputation (NRI) for study non-completers. All other 12 month outcomes were analyzed by ITT with last observation carried forward (LOCF) for non-completers. ACR, American College of Rheumatology; ASPIRE, Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; ERA, Early Rheumatoid Arthritis; NR, not recorded; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

to require a placebo control to confirm that the active comparator was indeed efficacious – thus the three-arm design in US301 and inclusion of a short-term placebo substudy in the recent Actemra versus Methotrexate Double-

Figure 2



Radiographic progression with methotrexate is also quite variable across protocol populations, best predicted by damage at baseline. Estimated yearly progression (baseline Total Sharp/Sharp van der Heijde score divided by mean disease duration) helps to illustrate differences in protocol populations and explains differences in change scores over the course of 12 and 24 months. ERA, ASPIRE, and PREMIER represent early disease populations. ASPIRE, Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; ERA, Early Rheumatoid Arthritis; MTX, methotrexate; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; TSS, Total Sharp/Sharp van der Heijde score.

Blind Investigative Trial In Monotherapy (AMBITION) [14] with tocilizumab.

If noninferiority is satisfied, efficacy is established and statistical superiority may then be queried and demonstrated. However, care must be taken to ensure that a protocol is not 'oversubscribed' (that is, enrollment of a number so large that small differences between therapies may be statistically significant but not clinically meaningful). This was illustrated by the comparison of methotrexate to leflunomide in MN302 [15]: differences of 1 in mean swollen joint count and 0.01 in mean Health Assessment Questionnaire-Disability Index (HAQ-DI) scores at 12 months. Thus, the requirement of two replicate trials for regulatory confirmation of statistical superiority has evolved [7].

Background disease-modifying antirheumatic drug trials

Early trials employed placebo controls. The last 'pure placebo' controlled RCTs in RA compared leflunomide with sulfasalazine versus placebo for 6 months (1998) [16], leflunomide with methotrexate versus placebo over 24 months with rescue of nonresponders on or after 4 months of treatment (1998) [5], and adalimumab monotherapy versus placebo in DMARD failure patients with rescue at 8 weeks (2000) [17]. Subsequent trial designs have used placebo only superimposed upon background therapy, typically methotrexate. Only in ATTRACT (Anti-TNF Trial in RA with Concomitant Therapy) [6], a 24-month RCT, was blinded treatment continued for 11 months before rescue. Thereafter, rescue of placebo treatment has been offered at 12 to 16 weeks [18-23] or mandatorily for nonresponders at 16 weeks in RAPID (RA Prevention of Structural Damage) 1 and 2 trials with certolizumab [24,25].

Over the past decade, the paradigm of 'step-up' or 'add-on' therapy has been used in several landmark RCTs. In these trials, patients with active disease despite DMARD therapy (again typically methotrexate) are recruited as partial responders following an incomplete or loss of therapeutic effect and then randomly assigned to the addition of study drug or placebo for 6 months. Although this trial design has been criticized [26], it offers several advantages, including the avoidance of exposure to pure placebo treatment and the fact that it does not require washout of prior DMARD therapy, thereby facilitating recruitment. A persistent concern has been whether patients enrolled in these add-on trials had previously responded to background therapy. As it would not be ethical to enroll subjects either having never responded to or no longer deriving benefit from background treatment to continue ineffective DMARD + placebo for an additional 6 months, it is unlikely that either patients or their treating physicians would have permitted their enrollment. Thus, equipoise, the principle that a subject be cognitively indifferent between two therapies, would not have been maintained.

Even with background therapy, the ethical issue of using placebo has prompted the use of a primary efficacy endpoint at 6 months, with demonstration of continued benefit in those 'successful responders', with still blinded or open-label treatment. FDA requirements have now been modified to 3 and 6 months for improvement in signs and symptoms with continued active treatment (open-label or blinded) and 6 to 12 months for assessment of structural damage and physical function, and 'maintenance of benefit' in those continuing active treatment over 12 to 24 months [27]. This allows placebo with or without background therapy to be 'rescued' on or after 2-3 months of treatment.

Following the Etanercept Phase 3 [3] and ATTRACT [6] trials, add-on therapy RCTs have comprised the majority of clinical development programs for adalimumab, abatacept, and rituximab. Despite differences in add-on treatment and timing of trials, demographics and disease characteristics of recruited patient populations have been remarkably similar: mean disease duration of 8 to 13 years, baseline DAS of 5.7 to 6.3, mean DMARDs failed of 2 to 3, mean prior methotrexate treatment of 2 to 4 years, and doses ranging from 15 to 19 mg/week. Two important criteria influence the outcome of this trial design: length of methotrexate treatment required at study entry and use of rescue therapy. Maximal responses to methotrexate (and other synthetic DMARDs,

including leflunomide and sulfasalazine) are evident on or after 6 months of treatment; those RCTs requiring at least 3 months of use of background therapy and/or offering rescue therapy after only 8 to 12 weeks are generally associated with higher placebo responses (Table 1) [28]. The observation that patients still accruing responses to background therapy may confound results was illustrated in a phase 2 RCT of an experimental interleukin-1-converting enzyme inhibitor [29] which failed to differentiate active from placebo treatment until those patients who had received methotrexate for less than 6 months were excluded, then demonstrating a dose response for the experimental therapy. Also important are potential drug-drug interactions that could explain improved therapeutic responses with combination therapy due to pharmacokinetic effects. The addition of cyclosporine to methotrexate was the first successful add-on trial in RA, with ACR20 responses at 6 months of 46% versus 16% in combination versus placebo + methotrexate, respectively [30]. However, when patients randomly assigned to placebo then received cyclosporine over the subsequent 6 months, ACR20 responses increased only to 21% [31]. Thus, the benefit of treatment in the first 6 months cannot be attributed to combination therapy but rather to a cyclosporine-mediated decrease in renal clearance of the active metabolite, 7-OH methotrexate, thereby increasing its half-life and accruing additional responses.

Recent trials have allowed a mixture of DMARDs as background therapy: both STAR (Safety Trial of Adalimumab in RA) [32] and ASSURE (Abatacept Study of Safety in Use with Other RA Therapies) [33] as large safety studies and the TOWARD (Tocilizumab in Combination with Traditional DMARD Therapy) trial [34], in which 40% had 'failed' methotrexate but which also included leflunomide and sulfasalazine among other DMARDs. Of importance, these trials have demonstrated efficacy of adalimumab [35], abatacept [20], and tocilizumab [34] across multiple background DMARDs. Although there is a clear regulatory precedent for using this trial design to demonstrate efficacy in RA, it is hoped it will be used progressively earlier in clinical development programs. Once safety (and efficacy) become evident in patients with a long duration of disease who have failed multiple DMARDs, it is appropriate to study a promising therapeutic agent in earlier disease populations, even DMARD-naïve patients, such as in ASPIRE [10], PREMIER [11], and AMBITION [14], prior to its approval.

Randomized controlled trials in anti-tumor necrosis factor failure patients

The evaluation of novel agents in a more real-world setting, after failure of TNF-I use, has added to our knowledge base. Examination of new therapeutic agents with background therapy in TNF-I-naïve patients as well as incomplete responders has characterized the safety and efficacy profile of abatacept (ATTAIN [Abatacept Trial in Treatment of Anti-TNF Inadequate Responders] [20] versus AIM [Abatacept in Inadequate Responders to Methotrexate] [19]), rituximab (REFLEX [Randomized Evaluation of Long-Term Efficacy of Rituximab] [21] versus DANCER [Dose-Ranging Assessment International Clinical Evaluation of Rituximab in RA] [22]), and tocilizumab (RADIATE [Research on Actemra Determining Efficacy after Anti-TNF Failures] [36] versus AMBITION [14]). Recently, three parallel RCTs have investigated the efficacy of tocilizumab in methotrexate, DMARD, or TNF-I incomplete responders [23,34,36]. Notably, responses in these trials range within a previously observed paradigm: in biologic-naïve patients, ACR20/50/70 responses from 59% to 71%, 40% to 44%, and 23% to 28%, respectively, compared with 50%, 28.8%, and 12.4%, respectively, in anti-TNF incomplete responders. Responses were similar whether subjects had failed one, two, or three anti-TNF agents.

Although open-label series have investigated the efficacy of 'switching' from one TNF-I to another, only one large controlled RCT studied responses to golimumab following failure to at least one TNF-I (GOlimumab After Former Anti-TNF Therapy Evaluated in RA [GO-AFTER]) [37]. In those who discontinued previous anti-TNF therapy due to lack of efficacy, 42.7% receiving 100 mg monthly achieved an ACR20 response at week 14 versus 17.7% with placebo. Nonetheless, subjects who had already 'failed' three TNF-Is were less likely to respond to a fourth agent.

Proof-of-concept trials

Proof-of-concept trials in RA require at least 3 months of treatment to allow sufficient time for improvement in manifestations of active disease to be demonstrated and confirm that benefit continues. This necessity has been demonstrated repeatedly when early studies of promising agents of only 1 month of duration were not confirmed with longer-term treatment over 8 to 12 weeks, as reported with several p38 mitogen-activated protein kinase inhibitors [38] and a TNF-α converting enzyme inhibitor [39], although a mechanistic explanation for loss of response remains elusive. Requiring 3 months of treatment has several important implications, including the necessity for toxicology studies of sufficient duration to 'cover' 12 weeks of dosing of a new agent in the clinic. As use of a pure placebo control as a comparator is now considered unethical, new therapies are introduced into the clinic superimposed upon background therapy, typically methotrexate. For synthetic agents, this means that drug-drug interaction studies must precede combination use to ensure no meaningful effects on half-life or metabolism of the background treatment, including nonsteroidal anti-inflammatory drugs (NSAIDs) as well as other commonly prescribed medications. It also means that a new therapy must be able to demonstrate benefit in a population of patients with active disease despite DMARD treatment, in general a more refractory population. In clinical development, it is therefore important to progressively study patients with earlier disease who have failed fewer DMARDs and who are more likely to be responsive to treatment in

order to fully characterize the efficacy of new therapies. Similarly, the observed safety profile of a promising therapeutic may differ in more robust patients with earlier RA and fewer comorbidities.

Methotrexate as an active comparator

Trials designed to show 'noninferiority' against an accepted efficacious therapy have long been used in rheumatology for iterative approvals with nonselective NSAIDs as well as cyclooxygenase-2 (COX-2)-selective agents [40]. Recent three-arm RCTs designed to compare monotherapy versus combination TNF-I + methotrexate treatment have importantly demonstrated superiority of the combination versus either monotherapy as well as superiority of anti-TNF versus methotrexate monotherapy for inhibition of radiographic damage [13]. Importantly, these three-arm RCTs have helped to better define 'real-world' use of TNF-Is and firmly established the additional clinical benefit of combination therapy when initiated simultaneously with methotrexate (and thus before methotrexate 'failure'). The early RA RCTs, ERA [12], ASPIRE [10], and PREMIER [11], have confirmed the impressive benefit of combination therapy in early disease, and TEMPO [13] demonstrated that it is not too late to see dramatic improvement in patients with 7 years of disease duration. Notably, methotrexate responses were high in this trial as 40% of subjects had received this DMARD within 6 months, thereby enriching the population with 'successful patients' who could tolerate the studied therapy.

In addition to potential synergy as well as additive efficacy attributed to different mechanisms of action, there are other potential explanations for the impressive benefit of combination biologic agent plus methotrexate. Methotrexate (as well as azathioprine and leflunomide) decreases the immunogenicity [41] of biologic agents and prolongs the half-life of anti-cytokine monoclonal antibodies (other than certolizumab), which may contribute to improved responses and/or responses that are more sustained.

Risks and benefits for use of placebo

In the placebo-controlled US301 trial, despite rescue of nonresponders on or after 4 months, withholding active treatment for this period resulted in losses of physical function that were not regained when active treatment was initiated [42]. Similarly, in an RCT of leflunomide added to background 'failed' methotrexate therapy [43], and in the open-label extension when those randomly assigned to placebo then received active therapy [44], despite similar ACR20/50 responses at 12 months, HAQ-DI scores never attained the same level of improvement. Mean changes in HAQ-DI (from baseline to 6 and 12 months) were −0.54 in patients who received combination therapy for the entire trial compared with −0.30 in those receiving combination therapy only during the second 6 months. Recognition of similar irreversible losses in physical function in other trials fortunately has resulted in a more limited use of placebo and an increasingly earlier use of rescue therapy.

There remains an important value of limited use of placebo as there exists a 'placebo response' that can be characterized. Patient-reported measures such as HAQ, pain, and patient global assessment of disease activity best differentiated responders and nonresponders in US301 [45], combined anakinra trials [46], and ATTRACT [47]. Nonetheless, there are a small number of subjects who receive placebo who are 'responders' by signs and symptoms, including physical function and radiographic outcomes [48]. These individuals have documented RA and cannot be characterized by differences in demographics or baseline disease activity, but they are few in number and responses generally wane over time.

Of interest, placebo responses appear to be higher with 'milder' active comparators, as Paulus and colleagues [49] demonstrated in early CSSRD (Cooperative Systematic Studies of Rheumatic Diseases Group) studies. This may be due, in part, to 'equipoise' as extensive discussions about risks and benefits of a new therapy may prime expectations of a very powerful intervention. Many other factors may also affect the placebo response and these are related to parenteral administration, including rapid onset of effect, infusion, and injection site reactions, which may result in expectation bias as well as unblinding. Most importantly, placebo has been necessary to prove inefficacy of many 'promising' agents [41], including anti-CD4 and anti-CD5 monoclonal antibodies. To miss this effect permitted by direct comparison to placebo would expose patients to a potentially toxic therapy lacking in efficacy.

Other trial designs

Other trial designs have been used to minimize or avoid the use of placebo controls. A frequent design in juvenile inflammatory arthritis (JIA) is the randomized withdrawal study, popular in pediatric populations in which the use of placebo is not ethical. This design includes an open-label run-in period in which all subjects receive active medication and subsequently those who respond to treatment are randomly assigned to blinded continuation or withdrawal of active medication. Flare in disease activity is measured as the primary outcome, and once it is documented, patients are eligible to receive open-label active therapy. This design was first used with etanercept [50] and has resulted in subsequent approvals for other biologic agents in JIA [51,52]. However, the use of randomized withdrawal studies in adult populations is more controversial, both from an ethical point of view and due to criticism that efficacy may not be definitively demonstrated.

Real-world randomized controlled trials 'treating to target'

Clearly RCTs do not mimic the real-world use of therapies: subjects enrolled in trials are a selected population with few of the comorbidities generally present in RA patients. Studies have confirmed that most patients followed in practice and enrolled in RA registries would not be eligible for clinical trials

[53,54]. There are several reasons for this, including the need to identify a responsive population to be able to demonstrate improvement successfully (for example, efficacy and inclusion/exclusion criteria that limit eligible subjects to those without medical conditions that could confound assessment of the safety of the agent). Patients whose RA is successfully controlled on current therapy will tell us little about the benefit of a new agent, nor would it be ethical to remove an efficacious treatment for purposes of ascertaining effect in an RCT. With the addition of so many new agents to our therapeutic armamentarium, it is no surprise that it is hard to find patients for enrollment in RCTs in RA, especially those on background therapy yet with sufficiently active disease. Thus, criteria defining 'active disease' have become more lenient, yet the ranges of baseline joint counts and disease activity in subjects enrolled in most recent trials are still remarkably similar. The introduction of a newly approved therapy into the clinic means it will be used in a broader patient population with more comorbid conditions and concomitant therapies. Efficacy outcomes may thus be less impressive than those observed in an RCT. Furthermore, rare safety events that were not observed in trials may become evident in postmarketing surveillance and/or longitudinal observational studies.

Although RCTs are the gold standard for evaluation of therapeutic efficacy, enrolled patient populations [53,54] and therapeutic protocols do not mimic those seen in the real world. The lack of flexibility to adjust treatment limits extrapolation of their results to real-world use. The advent of 'treatment to target' studies, while not designed for regulatory approval, provides an opportunity to study therapeutic regimens with the flexibility to change treatments - including the effect on patient expectations when treatments are changed. Trials published to date have not been blinded and their designs pose significant challenges: balancing randomization, inability to blind patients or investigators to treatment, lack of an intent-to-treat analysis, and inclusion of relatively small sample sizes. Treatment designs have progressed from initially looking for ACR and/or DAS responses to current goals of achieving 'low disease activity' and 'remission' [55,56] as well as assessing productivity within the home and workplace. The ongoing TEAR (Treatment of Early Aggressive RA) trial in the US is a blinded RCT using a 'treatment to target' approach, with results expected in the near future.

The FinRaCo (Finnish RA Combination Therapy) [56] trial introduced the paradigm of 'treating to target': allowing therapeutic titration in those not achieving a prespecified goal such as 'low disease activity' defined by a DAS of less than 2.4. Including COBRA (Combinatietherapie Bij Reumatoide Artritis) [57] and a large US combination trial [58], these were among the first to clearly demonstrate that early combination therapy was superior to monotherapy. Similarly, the TICORA (Tight Control for RA) [59] trial required aggressive escalation of traditional DMARDs with liberal use of intra-articular corticoidsteroid injections; 'remission' was achieved in 65% of subjects (defined as a DAS of less than 1.6).

The BeSt study was designed to demonstrate whether sequential DMARD monotherapy, step-up combination therapy, or an initial combination regimen including either prednisolone or anti-TNF therapy (infliximab) provided better and more sustained disease control in early RA. The opportunity to perform a trial in 'two dimensions' – using a disease target and a dynamic treatment strategy – led to several findings not previously observed in traditional RCTs. It confirmed that approximately 30% of the subjects receiving methotrexate monotherapy responded well but that further improvement (defined as a DAS of less than 1.4) can be achieved by an additional 40% of participants overall- higher than that achieved in most conventional RCTs. Additionally, the initial use of combination therapy with either TNF-I or DMARDs with high-dose steroids resulted in a more rapid onset of effect and more sustained control of disease activity, including structural benefit at 1 year compared with traditional DMARD monotherapy. Trials based on changes in treatment according to outcomes have demonstrated real-world benefit from aggressively targeting therapies as well as the superiority of biologic over nonbiologic DMARDs not observed in traditional RCTs.

Assessment of safety

Recent experiences with the selective COX-2 inhibitors [61] and other agents removed from the market due to documented liver toxicity [62] have underscored the importance of evaluating the safety of a new therapeutic prior to approval as well as of ensuring continued postmarketing surveillance. It is difficult to estimate adequate sample sizes in RCTs for assessment of safety, a lesson well learned when attempting to demonstrate that gastrointestinal safety of the COX-2s exceeded nonselective NSAIDs [61]. Furthermore, safety signals not evident in RCTs prior to approval may emerge in larger postmarketing trials or surveillance.

International Consensus for Harmonization guidelines for therapies of chronic diseases require that 1000 patients be exposed at the recommended dose, 300 patients for at least 6 months and 100 patients for at least 1 year [8]. Although the first two TNF-Is were approved for use only in patients with active RA, having failed multiple DMARDs with limited databases, their rapid acceptance and broader use prompted the FDA to require larger exposure populations prior to approval of adalimumab and abatacept. Ongoing post-marketing surveillance has further confirmed or identified safety 'signals' not observed in RCTs designed for regulatory approval. One or two cases of opportunistic infections, including tuberculosis or lymphomas, were evident in RCTs with etanercept and infliximab, but larger exposures in real-world use and trials in other clinical indications were required to identify signals for congestive heart failure [63],

demyelinating disorders [64,65], and cytopenias [66]. However, there is still great difficulty in sorting agent-specific risk from background disease risk as exemplified by cohort studies demonstrating no increase in or even decreased risk for congestive heart failure with use of TNF-I in RA patients [67]. Although some RCTs of current TNF-I (in populations other than RA) [68] have identified a possible signal for increased risk of lung cancer, this was not observed in any RA trials. Although a meta-analysis [69] of RCTs did support this association, a longitudinal cohort study evaluating over 13,000 patients with RA treated with biologic therapy (>97% of whom were TNF-I users) found no evidence for increased risk for solid tumors over RA patients receiving traditional DMARDs [70]. More recently, the ASSURE trial, an RCT designed to evaluate safety of abatacept, again identified a small but statistically increased signal for lung cancer in those randomly assigned to abatacept [33].

It is generally believed that 2,500 to 3,000 patient years per treatment are required to identify very rare adverse events [8]. Natilizumab (Tysabri™), a monoclonal antibody that inhibits the $\alpha 4\beta 7$ integrin and that is currently approved for treatment of multiple sclerosis and Crohn disease, provides a good example. Soon after approval, three cases of progressive multifocal leukoencephalopathy were reported [71], all occurring in 3,000 patients exposed to this agent in RCTs, an incidence of 0.1%. However, the incidence increased when examining subjects who received this agent in longer-term treatment or in combination with interferon-beta: 2 out of 2,000 treated more than 2 years (0.2%), 2 out of 589 receiving combination therapy (0.34%), and 1 out of fewer than 100 treated more than 3 years (more than 1.0%) [72]. An FDA-required detailed Risk Minimization Action Plan (RISKMAP) has allowed the reintroduction of this agent for the treatment of both clinical indications in the US, although new cases continue to accrue [73]. Such events may be due, in part, to the desire that efficacy be maximized in RCTs – often, biologic agents are administered in 'industrial strength' rather than pharmacologic or physiologic doses and/or at dosing intervals of less than the measured half-life of the agent, potentially resulting in accumulation.

As it has been difficult to identify relatively rare safety 'signals' of potential concern, large safety RCTs have been advocated. Two such RCTs, STAR [32] and ASSURE [33], superimposed use of the new therapeutic, adalimumab and abatacept, respectively, versus placebo on background DMARD therapy in RA. Although some have argued that such studies with a primary endpoint of safety cannot confirm efficacy of the test agent, they have identified the presence of certain safety concerns. As with a pilot and subsequent RCT, combination treatment with anakinra + etanercept resulted in less efficacy and more toxicity [46], and the combination of abatacept + TNF-Is in ASSURE [33] revealed an increased incidence of serious infections as well as lung cancer.

Registries established to monitor biologic therapies in RA have contributed significantly to our ability to confirm and further quantify risks potentially associated with traditional and biologic DMARD therapies and promise to do so in other rheumatic diseases. Thus, the FDA now recommends that new treatments be studied in well-characterized populations with adequate exposure and recommends labeling limited to use in these types of patients. It is expected that broader real-world use and subsequent trials in other populations will allow expanded use of the agent.

Conclusions and future directions

Much progress has occurred over the past decade in trial design in RA. These include the following:

- Establishment of a clear regulatory path to demonstrate efficacy of a new therapeutic
- The use of 'pure' placebo beyond 12 to 16 weeks has been demonstrated to be unethical. Thus, background therapy and early rescue have become regular practice.
- The recognition that identification of rare adverse events associated with a new therapeutic requires large-exposure databases and continuing postmarketing surveillance, including establishment of registries.
- Postapproval trials, especially 'treating to target' designs, are more relevant to identify real-world use of new and existing therapeutics.

Not all DMARDs or biologic agents behave as expected, and thus far biomarkers have not permitted earlier prediction of therapeutic efficacy. Although RCTs remain the gold standard for demonstrating efficacy of a new therapeutic, it is expected that shorter duration trials with better 'early' outcomes will facilitate efficient clinical development. Also, trials in patients with early RA, even undifferentiated arthritis, will push the envelope of treatment with current therapies and promising agents to come. We have much to look forward to in the next decade of clinical development in rheumatology.

Competing interests

VS is a consultant and/or advisory board member for the following companies: Abbott Immunology, Allergan, Almirall, AlPharma, Amgen Corporation, AstraZeneca, Bayhill, Bexel, BiogenIdec, Bioseek, BMS, CanFite, Centocor, Chelsea, Cypress Biosciences Inc, Dianippon Sumitomo, Euro-Diagnostica, Fibrogen, Forest Laboratories, Genelabs, Genentech, Human Genome Sciences, Idera, Incyte, Jazz Pharmaceuticals, Lexicon Genetics, Lux Biosciences, Merck Serono, Novartis Pharmaceuticals, NovoNordisk, Noxxon Pharma, Nuon, Ono Pharmaceuticals, Pfizer, Procter and Gamble, Rigel, Rigen, Roche, Savient, Sanofi-Aventis, Schering Plough, Scios, SKK, UCB, VLST, Wyeth, Xdx, Zelos Therapeutics. JS has no competing interests.

The Scientific Basis of Rheumatology: A Decade of Progress

This article is part of a special collection of reviews, *The Scientific Basis of Rheumatology: A Decade of Progress*, published to mark *Arthritis Research & Therapy*'s 10th anniversary.

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References

1. Williams HJ, Willkens RF, Samuelson CO, Alarcón GS, Guttadauria M, Yarboro C, Polisson RP, Weiner SR, Luggen ME, Billingsley LM, Dahl SL, Egger MJ, Reading JC, Ward JR: **Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial.** *Arthritis Rheum* 1985, **28:**721-730.
2. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, Trentham DE: **Efficacy of low-dose methotrexate in rheumatoid arthritis.** *N Engl J Med* 1985, **312:**818-822.
3. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ: **A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.** *N Engl J Med* 1999, **340:**253-259.
4. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, Weinblatt ME: **Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial.** *Ann Intern Med* 1999, **130:**478-486.
5. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, Fox R, Moreland L, Olsen N, Furst D, Caldwell J, Kaine J, Sharp J, Hurley F, Loew-Friedrich I: **Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group.** *Arch Intern Med* 1999, **159:**2542-2550.
6. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group: **Infliximab and methotrexate in the treatment of rheumatoid arthritis.** *N Engl J Med* 2000, **343:**1594-1602.
7. **FDA Guidance for Industry, Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis** [http://www.fda.gov/CDER/GUIDANCE/1208fnl.htm].
8. **European Medicines Agency - scientific guidelines** [http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm].
9. Khanna D, Park GS, Paulus HE, Simpson KM, Elashoff D, Cohen SB, Emery P, Dorrier C, Furst DE: **Reduction of the efficacy of methotrexate by the use of folic acid: *post hoc* analysis from two randomized controlled studies.** *Arthritis Rheum* 2005, **52:**3030-3038.
10. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group: **Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial.** *Arthritis Rheum* 2004, **50:**3432-3443.
11. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT: **The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment.** *Arthritis Rheum* 2006, **54:**26-37.
12. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK: **A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.** *N Engl J Med* 2000, **343:**1586-1593.
13. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators: **Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.** *Lancet* 2004, **363:**675-681.
14. Jones G, Gu JR, Lowenstein M, Calvo A, Gomez-Reino JJ, Siri D, Tomsic M, Blackburn R, Woodworth T, Sebba A: **Tocilizumab monotherapy is superior to methotrexate monotherapy in reducing disease activity in patients with rheumatoid arthritis: the AMBITION study [abstract].** *Ann Rheum Dis* 2008, **67 (Suppl II):**89.
15. Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gömör B, Van Den Bosch F, Nordström D, Bjorneboe O, Dahl R, Horslev-Petersen K, Rodriguez De La Serna A, Molloy M, Tikly M, Oed C, Rosenburg R, Loew-Friedrich I: **A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis.** *Rheumatology* 2000, **39:**655-665.
16. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C, Rosenburg R: **The European Leflunomide Study Group. Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial.** *Lancet* 1999, **353:**259-266.
17. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H: **Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed.** *Ann Rheum Dis* 2004, **63:**508-516.
18. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK: **Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial.** *Arthritis Rheum* 2004, **50:**1400-1411.
19. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Li T, Ge Z, Becker JC, Westhovens R: **Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial.** *Ann Intern Med* 2006, **144:**865-876.
20. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT, Dougados M: **Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition.** *N Engl J Med* 2005, **353:**1114-1123.
21. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC; REFLEX Trial Group: **Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks.** *Arthritis Rheum* 2006, **54:**2793-2806.
22. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, Racewicz AJ, van Vollenhoven RF, Li NF, Agarwal S, Hessey EW, Shaw TM; DANCER Study Group: **The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial.** *Arthritis Rheum* 2006, **54:**1390-1400.
23. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, Woodworth T, Alten R; OPTION Investigators: **Effect of interleukin-6 receptor inhibition with tocilizumab in**

patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008, **371:** 987-997.
24. Keystone E, Heijde DV, Mason D Jr., Landewé R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C, Pavelka K: **Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.** *Arthritis Rheum* 2008, **58:**3319-3329.
25. Smolen JS, Landewé RB, Mease PJ, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff MH, Burmester GR, Strand V, Vencovsky J, van der Heijde DM: **Efficacy and Safety of Certolizumab Pegol Plus Methotrexate in Active Rheumatoid Arthritis: The RAPID 2 Study.** *Ann Rheum Dis* 2008, in press.
26. Boers M: **Add-on or step-up trials for new drug development in rheumatoid arthritis: a new standard?** *Arthritis Rheum* 2003, **48:**1481-1483.
27. **FDA Arthritis Advisory Committee meeting: Tocilizumab July 29, 2008** [http://www.fda.gov/ohrms/dockets/ac/08/agenda/2008-4371a1-FDA-Final.pdf].
28. Strand V: **Counterpoint from the trenches: a pragmatic approach to therapeutic trials in rheumatoid arthritis.** *Arthritis Rheum* 2004, **50:**1344-1347.
29. Pavelka K, Kuba V, Rasmussen JM, Mikkelsen K, Tamasi L, Vitek P, Rozman B: **Clinical effects of pralnacasan (PRAL), an orally-active interleukin-1beta converting enzyme (ICE) inhibitor, in a 285 patient PhII trial in rheumatoid arthritis (RA) [abstract].** *Arthritis Rheum* 2002, **44:**S241.
30. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, McKendry R, Tesser J, Baker P, Wells G: **Combination therapy with cyclosporine and methotrexate in severe RA.** *N Engl J Med* 1995, **333:**137-141.
31. Stein CM, Pincus T, Yocum D, Tugwell P, Wells G, Gluck O, Kraag G, Torley H, Tesser J, McKendry R, Brooks RH: **Combination treatment of severe rheumatoid arthritis with cyclosporine and methotrexate for 48 weeks.** *Arthritis Rheum* 1997, **40:**1843-1851.
32. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA, Chartash EK: **Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis).** *J Rheumatol* 2003, **30:** 2563-2571.
33. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E: **Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study.** *Arthritis Rheum* 2006, **54:**2807-2816.
34. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, Woodworth T, Gomez-Reino JJ: **Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study.** *Arthritis Rheum* 2008, **58:**2968-2980.
35. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, Schattenkirchner M, Emery P, Burmester GR, Zeidler H, Moutsopoulos HM, Beck K, Kupper H: **Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study.** *Ann Rheum Dis* 2003, **62:**1168-1177.
36. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J, Kremer J: **IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF biologics: results from a 24-week multicentre randomised placebo controlled trial.** *Ann Rheum Dis* 2008, **67:**1516-1523.
37. Smolen J, Kay J, Doyle MK, *et al.*: **Golimumab, a new human anti-tnf-alpha monoclonal antibody, subcutaneously administered every 4 weeks in patients with active rheumatoid arthritis who were previously treated with anti-tnf-alpha agent(s): results of the randomized, double-blind, placebo [abstract].** *Ann Rheum Dis* 2008, **67(Suppl II):**50.
38. Damjanov N, Kauffman R, Spencer-Green GT: **Safety and efficacy of VX-702. a p38 MAP Kinase Inhibitor in rheumatoid arthritis [abstract].** *Ann Rheum Dis* 2008, **67(Suppl II):**125.
39. Fleischman R, Genovese M, Keystone M, Pavelka L, Durez M , Pavlik-Gaylord S*:* **Lack of efficacy with 3 oral dose levels of TMI-005(Apratastat), in subjects with active rheumatoid arthritis on a background of methotrexate: A phase 2 double blind, placebo controlled, parallel, randomized study [abstract].** *Ann Rheum Dis* 2006, **65(Suppl II):**339.
40. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, Verburg KM, Isakson PC, Hubbard RC, Geis GS: **Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison.** *Lancet* 1999, **354:**2106-2111.
41. Strand V, Kimberly R, Isaacs JD: **Biologic therapies in rheumatology: lessons learned, future directions.** *Nat Rev Drug Discov* 2007, **6:**75-92.
42. Olsen N, Schiff M, Strand V: **Alternate therapy with leflunomide (LEF) or methotrexate (MTX) after switch from initial treatment in patients with active rheumatoid arthritis (RA) [abstract].** *Arthritis Rheum* 1999, **42:**S241.
43. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, Luggen ME, Keystone E, Weisman MH, Bensen WM, Kaine JL, Ruderman EM, Coleman P, Curtis DL, Kopp EJ, Kantor SM, Waltuck J, Lindsley HB, Markenson JA, Strand V, Crawford B, Fernando I, Simpson K, Bathon JM: **Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial.** *Ann Intern Med* 2002, **137:**726-733.
44. Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, Luggen M, Keystone E, Bathon J, Kavanaugh A, Ruderman E, Coleman P, Curtis D, Kopp E, Kantor S, Weisman M, Waltuck J, Lindsley HB, Markenson J, Crawford B, Fernando I, Simpson K, Strand V: **Combination leflunomide and methotrexate (MTX) therapy for patients with active rheumatoid arthritis failing MTX monotherapy: open-label extension of a randomized, double-blind, placebo controlled trial.** *J Rheumatol* 2004, **31:** 1521-1531.
45. Strand V, Cohen S, Crawford B, Smolen JS, Scott DL; Leflunomide Investigators Groups: **Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis.** *Rheumatology* 2004, **43:**640-647.
46. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, Bekker P; 20000223 Study Group: **Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate.** *Arthritis Rheum* 2004, **50:** 1412-1419.
47. Antoni CE, Kavanaugh A, Manger B, Keenan G, Schaible T, Harriman G: **Responses to infliximab therapy in the ATTRACT trial assessed with the DAS score [abstract].** *Ann Rheum Dis* 2001, **60:**SII:171.
48. Van Holten J, Pavelka K, Vencovsky J, Stahl H, Rozman B, Genovese M, Kivitz AJ, Alvaro J, Nuki G, Furst DE, Herrero-Beaumont G, McInnes IB, Musikic P, Tak PP: **A multicentre, randomised, double-blind, placebo controlled phase II study of subcutaneously administered interferon beta 1a in the treatment of patients with active rheumatoid arthritis.** *Ann Rheum Dis* 2005, **64:**64-69.
49. Paulus HE, Egger MJ, Ward JR, Williams HJ: **Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. The Cooperative Systematic Studies of Rheumatic Diseases Group.** *Arthritis Rheum* 1990, **33:**477-484.
50. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, Sibilia J, Koné-Paut I, Gandon-Laloum S, LeBideau M, Bader-Meunier B, Mouy R, Debré M, Landais P, Prieur AM: **Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type.** *Arthritis Rheum* 2003, **48:**1093-1101.
51. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati

R, McIlraith MJ, Giannini EH, Martini A; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation: **Adalimumab with or without methotrexate in juvenile rheumatoid arthritis**. *N Engl J Med* 2008, **359:**810-820.
52. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA: **Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial.** *Lancet* 2008, **372:**383-391.
53. Sokka T, Pincus T: **Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission.** *J Rheumatol* 2003, **30:**1138-1146.
54. Greenberg JD, Kishimoto M, Strand V, Cohen SB, Olenginski TP, Harrington T, Kafka SP, Reed G, Kremer JM; Consortium of Rheumatology Researchers of North America Investigators: **Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort.** *Am J Med* 2008, **121:**532-538.
55. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D: **Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial.** *Lancet* 2008, **372:**375-382.
56. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S: **Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis.** *Lancet* 1997, **350:**309-318.
57. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: **Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group.** *Lancet* 1999, **353:**1568-1573.
58. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, Garwood V, Maloley P, Klassen LW, Wees S, Klein H, Moore GF: **Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications.** *N Engl J Med* 1996, **334:**1287-1291.
59. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D: **Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial.** *Lancet* 2004, **364:**264-269.
60. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC, Dijkmans BA: **Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial.** *Arthritis Rheum* 2005, **52:**3381-3390.
61. Strand V: **Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin?** *Lancet* 2007, **370:**2138-21351.
62. Goldkind L, Laine L: **A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: lessons learned from the bromfenac experience.** *Pharmacoepidemiol Drug Saf* 2006, **15:**213-220.
63. Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, Solomon DH: **Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis.** *Am Heart J* 2008, **156:**336-341.
64. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H: **Demyelination occurring during anti TNF therapy for inflammatory arthritides.** *Arthritis Rheum* 2001, **44:**2862-2869.
65. Robinson WH, Genovese MC, Moreland LW: **Demyelinating and neurological events reported in association with TNFa antagonism.** *Arthritis Rheum* 2001, **44:**1977-1983.
66. **Abbott Laboratories - Important Drug Warning** [http://www.fda.gov/medwatch/SAFETY/2004/HUMIRA_dhcp.pdf].
67. Wolfe F, Michaud K: **Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy.** *Am J Med* 2004, **116:**305-311.
68. Stone JH, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, Min YI, Specks U, Merkel PA, Spiera R, Davis JC, St Clair EW, McCune WJ, Ytterberg SR, Allen NB, Hoffman GS; Wegener's Granulomatosis Etanercept Trial Research Group: **Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial.** *Arthritis Rheum* 2006, **54:**1608-1618.
69. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: **Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials.** *JAMA* 2006, **295:**2275-2285.
70. Wolfe F, Michaud K: **Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study.** *Arthritis Rheum* 2007, **56:**2886-2895.
71. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P: **Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease.** *N Engl J Med* 2005, **353:**362-368.
72. Kappos L, Bates D, Hartung HP, Havrdova E, Miller D, Polman CH: **Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring.** *Lancet Neurol* 2007, **6:**431-441.
73. **FDA MedWatch - 2008 Safety Alerts for Human Medical Products** [http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tysabri2].
74. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB: **Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial.** *Br J Rheumatol* 1997, **36:**1082-1088.
75. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Cannon GW, Spencer-Green G, Finck BK: **Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.** *Arthritis Rheum* 2002, **46:**1443-1450.