Review

Risk of Failure of a Clinical Drug Trial in Patients with Moderate to Severe Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We conducted a systematic review to determine the risk of drug failure in clinical testing with patients with moderate to severe rheumatoid arthritis (RA).

Methods. Therapies for RA were investigated by reviewing phase I to phase III studies conducted from December 1998 to March 2011. Clinical trial success rates were calculated and compared to industry standards. Trial failures were classified as either commercial or clinical failures. The exclusion criteria for drugs in this study: drugs that were started in phase I studies prior to January 1998 for this indication; or studies that enrolled patients who were methotrexate-naive and/or had failed biologic therapy.

Results. A search in clinicaltrials.gov and approved drugs for the indication yielded a total of 69 drugs that met the study criteria. The cumulative success rate was determined to be 16%, which is equivalent to the industry standard of 16%. For each phase, the frequency of clinical failures exceeded commercial failures. Clinical studies equally comprised investigations of small molecules and biological agents, but biologics seemed to exhibit a higher success rate overall.

Conclusion. Clinical trial risk in RA with the 84% failure rate reported here is at par with industry performance and phase II success rate seems to be highly predictive of phase III success. (J Rheumatol First Release Sept 1 2012; doi:10.3899/jrheum.120005)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CLINICAL TRIAL RISK SUCCESS RATE
BIOLOGICS DISEASE-MODIFYING ANTIRHEUMATIC DRUG

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory autoimmune disease affecting 0.5%–1% of the general US population[1]. Although it may affect people of all ages, RA prevalence rates increase progressively with age, with a peak onset in the fifth decade and a higher incidence rate in women than in men[2]. Without adequate early treatment, RA will cause permanent joint damage as well as serious functional disability leading to reduced quality of life[3]. The severe form of RA is associated with premature mortality due to cardiovascular disease, infections, respiratory disease, and some malignancies[4,5]. The American College of Rheumatology Subcommittee Rheumatoid Arthritis recommends that patients with suspected RA confirm the diagnosis and initiate therapy with disease-modifying antirheumatic drugs (DMARD) within 3 months of presenting symptoms[6]. Low-dose methotrexate (MTX) is the main choice among physicians. Although MTX shows reduced morbidity measures, longterm conventional DMARD therapy is only effective in a proportion of patients[8]. The remainder of patients are therefore still at risk for disease progression and require additional treatment.

From 1998 to 2009, the number of therapeutic alternatives for RA has increased, with 10 new drug approvals. Almost all are biologic agents developed against specific targets that play a role in RA pathogenesis, including tumor necrosis factor (TNF)-blocking agents, interleukin 1β (IL-1β)-blocking recombinant soluble receptor, T cell costimulatory receptor-blocking protein, B cell-depleting monoclonal antibody, and antibody against IL-6 receptor[9]. With the rather high number of approvals, RA holds an impressive record during a time when the overall productiv-

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ity of the pharmaceutical industry, as measured by the number of new drugs being introduced to market, has declined[9]. Examination of clinical trials success rates in this disease area would help to determine how to mitigate clinical trial risk for investigational drugs that are currently being evaluated.

In this systematic review, drug candidates intended to treat patients with moderate to severe RA were reviewed. Selected drug candidates had clinical study sites in the United States, and testing was done from January 1998 to March 2011. This is the first study of its type, to our knowledge, to quantify the clinical trial risk in this disease area. To determine the risk of clinical trial failure in RA therapy, successful drugs were compared against failed drugs for each phase of clinical testing. The nature of failure (clinical vs commercial) was examined for each phase along with the type of therapy used (monotherapy vs concomitant therapy). Drug candidates were also classified as biologics or small molecules to elucidate trends between drug properties and clinical success.

MATERIALS AND METHODS

Study eligibility. Phase I, II, or III clinical studies in second-line therapy of moderate to severe RA from January 1998 to March 2011 were included in the analysis. Approved drugs with phase I trials conducted before 1998 were omitted from our study. Patients who were MTX-naive and patients who had failed biological treatment were also excluded. Moreover, all trials were industry-sponsored and had US sites. Drugs that were administered as monotherapy as well as concomitant therapy were eligible. A drug was considered a "line extension" if it had been previously approved for a different indication and subsequently entered testing in RA. Phase I/II trials were considered as phase I, while phase II/III trials were considered as phase II.

Databases and online tools. The Website clinicaltrials.gov was the main source of data for our study. Press releases served as a supplementary tool in compiling a list of eligible drug programs. The following search terms were used: "rheumatoid arthritis + clinical trial," "rheumatoid arthritis + press release," "rheumatoid arthritis + press news," and "rheumatoid arthritis + trial results."

Clinical trial outcome classification. Phase I and I/II clinical testing was classified as a "success" if the drug advanced to phase II. Phase II clinical testing was classified as a "success" if the drug advanced to phase III. Phase III clinical testing was classified as a "success" if the US Food and Drug Administration (FDA) approved the compound and it remained on the market as of March 2011.

Classification of clinical trial failure. Clinical trial failure was separated into clinical and commercial failure. A clinical failure was defined as one where a drug failed to meet its primary endpoint in phase II or phase III, or had significant safety issues during any of the phases. If a clinical trial was "withdrawn" or a drug was withdrawn from the market, it was considered a clinical failure. Commercial failure, on the other hand, was defined as a drug program that showed no indications of clinical failure in press releases or conference proceedings yet no further clinical testing of the drug was conducted in 2 or more years. Competing drug programs, lack of financing, and revisions of revenue forecast for the drug candidate could all result in commercial failures. Drug programs that completed a trial in the last 2 years without any indication of clinical failure were considered "unclassified/unknown" and were not included in the analysis.

Clinical trial success rate. The clinical trial success rate was calculated by determining the percentage of successful trials out of the total number of trials in a particular phase, as follows:

Success rate for phase x = (number of drug candidates that successfully completed phase x)/ (total number of drugs that completed phase x)

The "number of drug candidates that successfully completed phase x" refers to the number of drug candidates that successfully completed phase x and moved on to phase x + 1 (and/or phase x + 2). The denominator includes the number of drugs that completed phase x but did not move on to phase x + 1. Cumulative rates refer to the probability of completing the current clinical trial and any preceding clinical trial phase successfully (i.e., the product of probabilities). For example, a drug that is currently in phase III is a success for both phase I and phase II given that those trials were completed in the specified time period of this study.

Drug and company classifications. Drugs were classified as small molecules or biologics. Biologics were defined in accord with the FDA guidance stating that "biological products are generally derived from living material — human, animal, or microorganism — are complex in structure and thus are usually not fully characterized"[10].

Phase I ownership of each drug entity was categorized as "biotech" or "pharmaceutical." Firms were considered biotechnology companies if they were listed in the NASDAQ biotechnology index at the time of phase I start of the drug program. Companies that were not listed on the index and had a market capitalization over $1 billion US were classified as pharmaceutical companies. Companies that did not meet the above criteria were not classified.

RESULTS

An initial search for drug candidates in RA on clinicaltrials.gov yielded over 1200 hits, comprising over 85 drug candidates and multiple hits per drug. A list of 69 drug candidates was found to meet the specified criteria of this study. Fifty-nine drugs had successfully completed phase I between 1998 and March 2011, 10 drugs had successfully completed phase II, and 6 drugs had successfully completed phase III. The approved drug candidates that fit within our study criteria were Humira (adalimumab), Rituxin (rituximab), Orencia (abatacept), Simponi (golimumab), Cimzia (certolizumab pegol), and Actemra (tocilizumab).

Success rate for each phase was calculated and compared to industry standards. The latter were extracted from previously reported studies for industry as a whole, encompassing many therapeutic areas[11]. As shown in Figure 1, the phase I success rate was calculated to be 88%, much higher than the industry standard of 64%. The phase II success rate was 22%, which is significantly lower than the industry standard of 39%. Phase III yielded a success rate of 86% for this indication, 66% for industry. Cumulatively, the success rate for RA was 16%, which is at par with the industry standard of 16%.

Drugs were separated into clinical and commercial failures based on the reasons for the halt of the drug's progress. For phase I failures, 3 were commercial and 2 were clinical. Phase II had the highest number of failures overall, which aligns with the lower success rate (transitional probability) depicted in Figure 1 (14 were due to clinical reasons and 8 were due to commercial reasons). Only 1 failure was

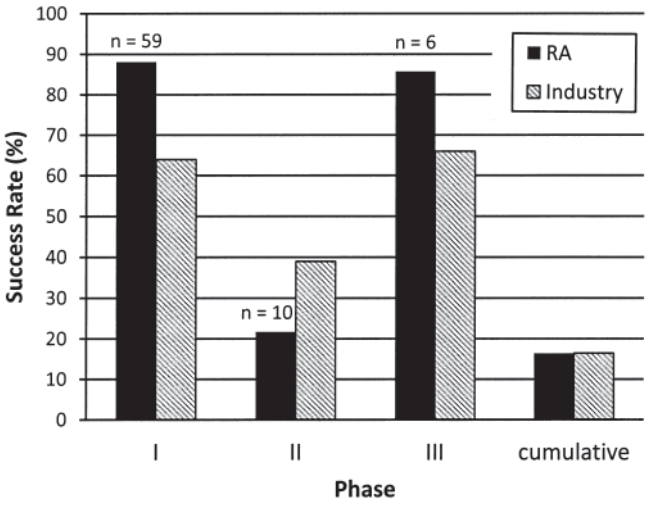

Figure 1. Clinical trial success rates in moderate to severe rheumatoid arthritis (RA). Drugs that entered phase I clinical testing during or after 1998 were tracked until March 2011. "Success rate" refers to the likelihood that a drug would complete the current phase and advance to the next phase of clinical testing (or approval if currently in phase III) based on the collected dataset. Industry pass rates are extracted from previously published studies.

observed for phase III and it was clinical (owing to ocrelizumab). Overall, there were more clinical failures than commercial failures (17 clinical vs 11 commercial), and the commercial failures seemed to be more concentrated early in clinical testing (phase I and II).

Figure 2 illustrates the success rate of each phase classified by monotherapy and concomitant therapy. Drugs that used both concomitant and monotherapy regimens were included in both groups. There were no significant differences in success rates for all 3 phases when comparing the 2 treatment regimens. For phase I, monotherapy showed a success rate of 88% versus 89% for concomitant. For phase II, the success rate for monotherapy was 27% in comparison to 24% seen for concomitant therapy. A 100% success rate was seen for monotherapy in phase III and 86% for concomitant therapy. Overall, a greater number of drugs were investigated as concomitant therapy in comparison to monotherapy.

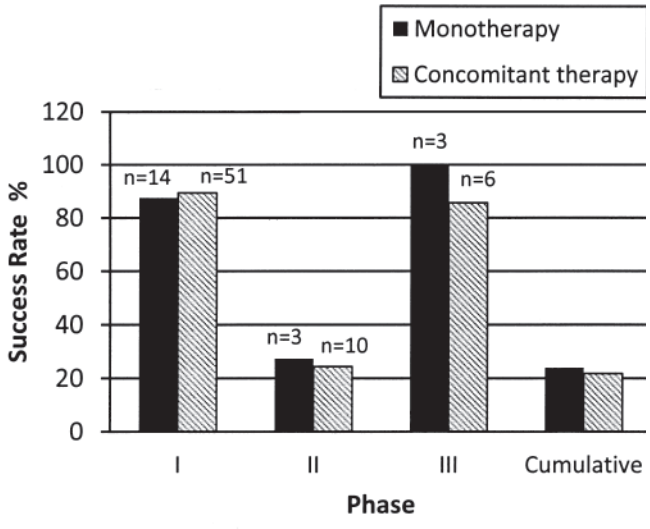

Figure 2. Clinical trial success rates in rheumatoid arthritis based on drug regimen (monotherapy vs concomitant therapy). Drugs that used both regimens were double-counted.

Properties of drug candidates are examined in Figure 3, and their respective transitional probabilities were calculated. Phase I showed an equivalent success rate for small molecules and for biologics at 88%. However, in phase II, biologics had a success rate of 41%, while small molecules had a mere 5%. A 100% success rate was seen for biologics in phase III, and no small molecules were investigated in this phase. Overall, a cumulative success rate of 31% was seen for biologics, and all approved drug candidates included in this analysis were biologic agents. This illustrates the success of biologics in comparison to small molecules in this indication.

Drug sponsorship was classified into pharmaceutical and biotechnology companies based on phase I ownership. Both types of companies showed very similar transitional probabilities for all clinical study phases, as depicted in Figure 4. The numbers of successful drug candidates were also distributed very similarly across the 2 types of industry sponsors. The cumulative transitional probability was 18% for pharmaceutical drugs and 20% for biotechnology drugs. Drug sponsorship, therefore, does not seem to influence the success rate for therapies of moderate to severe RA.

DISCUSSION

In our study, the clinical trial success rate for moderate to severe RA was found to be 16%, which is equivalent to the industry standard. This means that out of 6 drug candidates clinically investigated in this disease area, only one will make it to market successfully. Previously reported success rates (calculated using the same methodologies as in this analysis) for other disease areas include 11% for non-

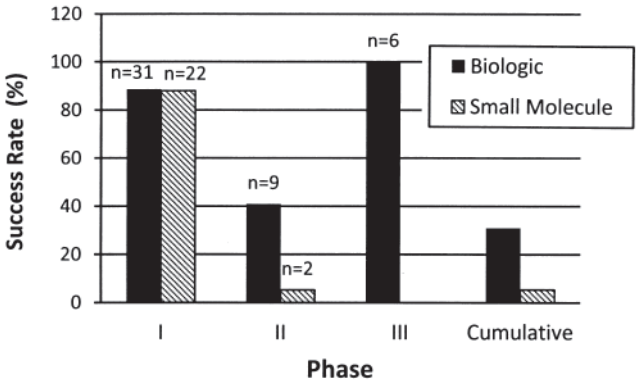

Figure 3. Clinical trial success rates in rheumatoid arthritis based on drug property (biologic or small molecule).

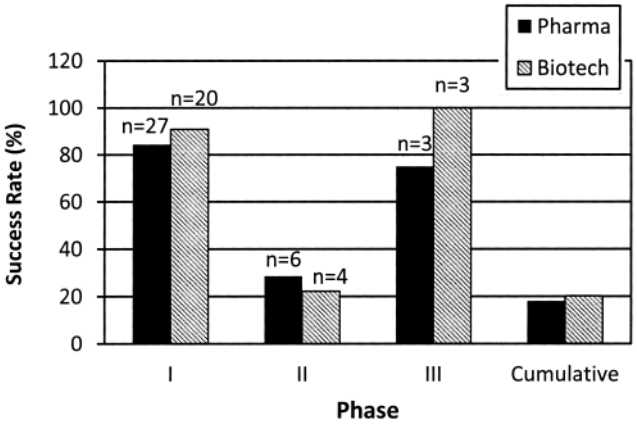

Figure 4. Clinical trial success rate in rheumatoid arthritis based on whether the drug's phase I ownership belonged to pharma or biotech company.

Hodgkin's lymphoma[12], 19% for Crohn's disease[13], and 16.7% for human immunodeficiency virus[14]. Even with a high number of drug approvals in the last decade, success rates in RA clinical studies are not higher than industry standards, and it is phase II transitional probability that seems to dictate the cumulative success rate.

Generally, a high success rate is expected for phase I, given that these trials are concerned with pharmacokinetic and pharmacodynamic properties of the drug entity and overall safety of the compound. Currently, phase Ib studies are conducted by companies to determine efficacy of molecules at an earlier stage in testing. These studies may decrease overall success rates in phase I.

The trend of a lower phase II success rate followed by a higher phase III success rate is the ideal scenario for drug development. It is imperative to eliminate unsuccessful drug candidates early in clinical testing so that resources can be allocated to drug candidates with more potential. This, in turn, increases the return on investment for the companies that are involved in clinical development.

The highest number of failures was seen in phase II, with significantly more clinical failures in comparison to commercial failures. The data sources used in our study and the unsophisticated methods for identifying commercial failures may pose a limitation to this analysis. It is possible that clinical failures were not reported in the resources used for this analysis and therefore they were actually identified as commercial failures. It is also possible that several studies have been terminated but not publicly. This may lead to an even higher number of clinical failures than determined here. In such a scenario, the high rate of clinical failure in phase II could be due to poor animal models that do not translate well into clinical testing.

Concomitant therapy seems to be more prevalent in RA in comparison to monotherapy. However, when success rates were calculated for both treatment regimens, no significant differences were seen for each phase. This could be because drugs that use monotherapy and concomitant treatment were double-counted in the analysis and therefore allowed a higher success rate for monotherapy (which has a lower prevalence overall).

The majority of combination therapies included MTX, with some studies including hydroxychloroquine, sulfasalazine, leflunomide, and other DMARD. Despite the risk of toxicity and adverse effects, combination treatments with DMARD have shown greater clinical utility as well as cessation of disease progression in RA[15]. This explains the high overall frequency of concomitant treatment in comparison to monotherapy. The benefits of monotherapy include simpler study design and lack of drug-drug interactions as well as reduced combined side effects. Concomitant therapy may appear to be the more attractive option because of the lack of combined immunosuppression offered by DMARD, such as MTX, when administered alongside the novel agent. Biologics encompassed the majority of investigational drug candidates in our study and exhibited a higher success rate in comparison to small molecules. In addition, all approved drugs included in our study were also biologics. It has been predicted by many in the pharmaceutical industry that biological DMARD therapy would soon be replaced by oral small molecules; however, developing small molecule therapies with adequate efficacy and safety has proved to be extremely difficult[9]. Nevertheless, 2 small-molecule drug classes, janus-associated kinase and spleen tyrosine kinase inhibitors, are currently being evaluated in late clinical testing[9]. It is possible that the high success rate of phase III could extend to small molecules, but because of the safety concerns associated with them (e.g., hypertension and altered liver function), their clinical significance remains to be evaluated[9,16].

Our systematic review shows that there is a higher predictive value associated with phase II that may lead to a high phase III success rate in RA. Such results were not seen in indications such as Crohn's disease and non-Hodgkin's lymphoma[12,13].

Our review of the reported clinical trials for RA suggests that even with many established drugs on the market, novel disease-targeting and thorough understanding of disease pathogenesis is required to overcome the 84% failure rate in drug development. Phase II results appeared to be highly predictive of phase III outcome, suggesting that in RA, intermediate data can be a reliable tool in forecasting future study success.

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