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Reducing clinical trial risk in multiple sclerosis

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ABSTRACT

Objective: To determine the risk of clinical trial failure for new drugs in multiple sclerosis (MS) and to identify factors that could improve outcomes.
Methods: We collected data on compounds that were tested in MS from Phase I to Phase III clinical trials between 1998 and January 2015. Clinical trials success rates were calculated and compared to industry standards. The exclusion criteria for the drugs in this study were: drugs that commenced Phase I in MS prior to 1998, non-industry conducted trials, trials testing non-disease modifying drug treatment, and trials testing combinations of drugs already approved by the FDA.
Results: Fifty-three distinct drugs met our inclusion criteria. The cumulative success rate for MS drugs was 27%, almost triple the 10% industry rate. Clinical trial success rates in MS surpass that of industry across all phases. Phase II clinical trials completed in a "Relapsing MS" population were most successful in predicting Phase III clinical trial success. Small molecules were found to have a higher overall success rate compared to biologics; however, both drug technologies largely pursue different molecular targets. Drugs that were previously FDA approved for another indication and were subsequently tested in MS had lower success rates than drugs that had no previous FDA approval history.
Conclusions: Overall, MS enjoys almost triple the clinical trial success rates of other disease areas. In addition, small molecules are superior to biologics in MS and novel drugs are superior to drugs with a previous FDA approval history outside MS.

1. Introduction

The rapid expansion in the armamentarium of multiple sclerosis (MS) therapeutics is widely considered an exemplary achievement of modern drug development. In the span of approximately 20 years, therapeutic options for patients with MS increased from solely steroids to eleven FDA approved disease-modifying therapies (DMT's), ranging from injectable biologics to the more recently approved small molecule drugs (Tavazzi et al., 2014). It is considered even more remarkable that the majority of the drug approvals occurred during a time when the FDA approved 25% fewer drugs on average than in past decades, despite increases in research and development spending (Cohen, 2005; Hay et al., 2014). Although the sudden progress in DMT's for MS is encouraging, the therapeutic landscape for MS is far from complete as there is a particular dearth of therapeutics indicated for progressive MS. Additionally, although studies have quantified clinical trial risk in the drug industry as a whole, (Cohen, 2005; DiMasi et al., 2010) to our knowledge, no study has quantified the clinical trial success and attrition within this particularly "successful" disease area. Therefore, the aim of our study was to quantify clinical trial risk in MS as it compares to failure rates in the drug industry as a whole and to highlight clinical trial risk factors specific to MS with the view to improve future decision making in MS drug development. The study applies methodology reported previously in several publications examining clinical trial attrition in disease areas such as prostate cancer, lung cancer, Crohn's disease and rheumatoid arthritis (Parker and Clare Kohler, 2010; Parker et al., 2011', 2012; Jayasundara et al., 2012; Falconi et al., 2014; Tenuta et al., 2014).

2. Methods

2.1. Study eligibility

Utilizing the methodology of previously published papers on disease-area specific clinical trial attrition (Parker and Clare Kohler, 2010; Parker et al., 2011, 2012; Jayasundara et al., 2012; Falconi

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et al., 2014; Tenuta et al., 2014), Phase I, II and III clinical trials evaluating investigational drugs for the treatment of multiple sclerosis in its varying subtypes—relapsing-remitting (RRMS), secondary-progressive (SPMS) and primary-progressive (PPMS)—were analyzed. Clinical trials for drugs that were intended to treat secondary complications of MS, such as spasticity, fatigue and cognitive impairment, were excluded from the study. Only drugs being developed as "disease-modifying therapy" were included. Additionally, the trials must have been industry sponsored and Phase I trials must have been completed after 1998. Drugs being tested in combination with other drugs were included so long as one of the drugs being tested was not already FDA approved for the purposes of MS.

2.2. Database and online tools

The primary information source used for this study was the public, online, clinical trial database: http://clinicaltrials.gov/. "Multiple sclerosis" was used as the primary search term and the results were filtered based on the above stated inclusion criteria. Additional research outside the scope of this database was completed using publically available Internet resources, press releases, and online journals/periodicals (accessed through University of Toronto Libraries).

2.3. Classification of cinical trial success

A simple, transparent, and previously established rule was applied to classify clinical trial outcomes (Parker and Clare Kohler, 2010; Parker et al., 2011, 2012; Jayasundara et al., 2012; Falconi et al., 2014; Tenuta et al., 2014). In order to be considered a Phase I clinical trial success, a compound must have completed a Phase I clinical trial and subsequently transitioned to a Phase II clinical trial. Similarly, a compound was classified as a Phase II clinical trial success if it subsequently moved on to Phase III, and a Phase III clinical trial success if the compound was granted Food and Drug Administration (FDA) approval for MS. Compounds in Phase I/II clinical trials were considered to be in Phase I, and compounds in Phase II/III clinical trials were considered to be in Phase II. Therefore, a compound that completed a Phase I/II clinical trial and moved on to Phase II/III clinical trials was considered a Phase I success. Additionally, compounds transitioning from Phase IIa to Phase IIb were not considered Phase II successes. Similarly, a transition from Phase II to Phase II/III was considered a transition from Phase IIa to Phase IIb, and therefore not considered a Phase II success.

Compounds with registered Phase II and/or Phase III clinical trials but missing Phase I clinical trials registered on clinicaltrials.gov were "backfilled" as Phase I clinical trial successes as long as the Phase II trial began no earlier than the year 2000. Similarly, compounds undergoing Phase III clinical trials with absent Phase II clinical trials were backfilled as Phase II clinical trial successes. This was typically the case if the compound with the missing Phase II was analogous to a previously tested drug (with Phase II data), or the drug was being tested in a new disease subtype after already undergoing a Phase II trial in another MS subtype.

In exceptional cases, a drug was considered a Phase II success if it moved on to Phase III based on the interim date of an ongoing Phase II trial. After applying these criteria, the clinical trial transition probability was calculated by determining the percentage of unique drugs that successfully completed a phase of development out of the total number of drugs tested in a particular phase of development, as demonstrated using the following equation:

$$\text{Transition probability for Phase } x = \frac{(\#\text{ of drugs passed to Phase } x+1)}{((\#\text{ of drugs that passed to Phase } x+1)+(\#\text{ drugs that failed at Phase } x))}$$

Data was collected from clinicaltrials.gov up until 1 January 2015, at which point the dataset was officially closed.

2.4. Classification of clinical trial failure

Clinical trial failures were categorized as either *clinical* or *commercial*. A compound was deemed a *clinical* failure if it failed to progress to the next phase of clinical testing because the most advanced trial raised safety concerns and/or failed to meet it's primary endpoint. Conversely, a compound was considered a *commercial* failure if it failed to progress to a subsequent clinical trial within two years of the most recent trial completion date, despite press reports or publication of positive clinical trial results.

Occasionally, pharmaceutical companies chose to discontinue clinical trials for an efficacious compound in order to develop a newer, analogous agent to be tested in its place. In this event, the first compound was considered a commercial failure, despite its proven efficacy, and the analogous agent was treated as a separate entity undergoing it's own stream of clinical trials. Additionally, because this study includes only industry-sponsored trials, drugs were considered failures if industry sponsored trials were abandoned whether or not a public institution chose to conduct further testing.

2.5. Compound classification

Compounds were classified as either small molecules or biologics. Biologics were determined in accordance with the FDA definition, which includes "vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins" (FDA, 2015). Any active compound that did not fall within this definition was considered a small molecule. Compounds were categorized as previously FDA approved drugs if they received approval for another indication prior to undergoing MS clinical trial testing. In order to be included in this category, the drug being tested for MS must have been in the exact form as the drug that was FDA approved; metabolites of FDA approved drugs or similar compounds were categorized as drugs with "No prior FDA approval history".

2.6. Classification of clinical trial study population

Clinical trial study populations were determined for Phase II and Phase III clinical trials using the trial inclusion and exclusion criteria listed on clinicaltrials.gov. Considering Phase I studies were completed in a wide variety of study populations, including healthy volunteers, we chose not to classify Phase I study populations. Phase II and Phase III clinical trials enrolled one of the following study populations: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), "Relapsing MS" (RRMS or SPMS with relapses), or primary progressive MS (PPMS). A given compound may have undergone more than one Phase II or III clinical trial, each in a separate study population; in this event, the drug was treated as a separate entity for each of the subtypes it was investigated in. For example, a single drug may undergo a distinct series of clinical trials enrolling patients with one MS subtypes (i.e. RRMS) and another enrolling patients with a different MS subtype (i.e. PPMS). In this event, the compound may be successful in one of the subtypes (i.e. RRMS) while failing in the other (i.e. PPMS),