

The clinical application of medical science research: investment and duration

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Abstract

Several obstacles hamper the clinical application of basic medical scientific research. Of reports published in 6 major basic science journals between 1979 and 1983, only 27 were translated into published randomized trials within 10 years of their initial publication. To evaluate changes in frequencies and time required for the clinical application of basic medical science research over a 10-year period, we conducted a literature search of articles published between 1989 and 1993 in eight major medical journals containing words related to clinical application in their titles or abstracts. Articles were evaluated based on whether their findings resulted in clinical application. Primary outcome was the time until translation to clinical application, which was defined as drug approval or publication of positive randomized trials. Of the 202 medical science articles identified, clinical application was eventually reported for 22. Mean time until clinical application was 22.4 years, which was longer than the 10 years previously reported ($p < 0.021$). No marked differences were noted in background content between the articles that resulted in clinical application and those that did not, except for the implication of promising technologies. The prevalence of clinical application was lower and the duration until clinical application was longer than 10 years ago. Promising technologies should be carefully evaluated before study funds are allocated for clinical application.

Introduction

Numerous obstacles hamper the clinical application of medical research. Drug development, for instance, is reported to take upwards of 10 years and can cost nearly a billion United States (US) dollars [1]. Further, the cost of developing new drugs is increasing [2,3]. Promising technologies must first undergo preclinical study in the laboratory, which requires 3 to 6 years [4]. Candidate drugs must then undergo Phase 1 to 3 clinical trials in humans, which require 6 to 7 years [4]. The success rate for clinical approval is extremely low, with only 1 in every 5,000 compounds receiving approval from the Food and Drug Administration (FDA) [5]. In addition, the volume of pharmaceutical research and products decreased between 1990 and 2004 [6].

Ioannidis *et al.* found that, of all reports published in 6 major basic science journals between 1979 and 1983, only 27 were translated into published randomized trials within 10 years of their initial publication [7]. These authors also reported that medical studies cited more than 1000 times required 24 years to reach clinical trials [8]. Since the 1990s, the number of biotechnology-based drugs has increased [9]. Further, since the mid-1990s, a well-established process for drug discovery has been used by pharmaceutical companies [10]. Changes are anticipated in the near future regarding the medical science research field and the period required to reach clinical application. However, despite the rapid progress being made in this field, to our knowledge, no comprehensive studies in the past decade have examined the clinical application of basic medical science research. Our aim of this study is

to evaluate changes in frequency and time until clinical application of medical science research over a 10-year period.

Materials and methods

Inclusion criteria

Inclusion criteria were articles that resulted in clinical application that were published between January 1989 and December 1993 in eight major medical science journals. These eight journals consisted of the five used in the previous study [7] (*Nature*, *Cell*, *Science*, *The Journal of Experimental Medicine* and *The Journal of Clinical Investigation*) and three newly selected due to their high-impact factors (*Nature Biotechnology* and *Nature Genetics* derived from *Nature*, and *Proceedings of the National Academy of Sciences of the United States of America*).

As in Ioannidis *et al.* study, articles containing the following in their title or abstract were identified: therapy, therapies, therapeutic,

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therapeutical, prevention, preventive, vaccine, vaccines, or clinical [7]. From these articles, original articles clearly stating that their findings might be clinically applicable as either or both prophylactic or therapeutic agents were selected. Eligible technologies included substances, antibodies, vaccines, gene therapies and combination therapies. In the previous study, although technical devices and other non-pharmacological interventions were included, they were not considered promising technologies [7]. These two technologies were therefore excluded from the present study and pharmaceutical agents were focused on.

Technologies still at the experimental stage (molecular, cellular, animal and early nonrandomized human trials) that did not have prior application in humans for a specific purpose were also included. Articles regarding new applications of an established technology were also included.

Exclusion criteria

The following were excluded: articles with no description of clear clinical potential in the abstract; reviews; editorials; comments; news articles; articles regarding mechanism of action, pathophysiology, diagnosis, technical devices or non-pharmacological intervention; articles regarding agricultural or veterinary applications; and articles overlapping with other articles.

Screening

PubMed (National Center for Biotechnology Information) was searched for articles that failed to meet the inclusion criteria using two steps of screening. The first step of screening was conducted based on title and abstract and the second on the full text of promising articles based on the selection rules of the reviewer. If a decision on inclusion could not be made, reviewers discussed the article in pairs and disagreements were resolved by consensus.

Data extraction

The following information was extracted from each eligible article: journal name, publication year, author information (name and institute), study design, promising technology, whether a specific technology or category of technologies was involved, anticipated application (therapeutic, preventative, or both), and disease target (cancer, nerve, cardiology, metabolism/endocrine secretion, or other). We also extracted information regarding industry involvement, defined as reported author affiliation, financial support unconnected to an author (industry funding received when no authors belonged to industry), provision of technology unconnected to an author (technology provided by industry when no authors belonged to industry), or none reported. In Ioannidis *et al.* study, the anticipated application was categorized as therapy, preventative, vaccine, or both therapy and prevention [7]. In the present study, given that some vaccines have a role in both therapy and prevention, we used categories of therapy, prevention, and both therapy and prevention.

Identification of human studies and determination of clinical use and development status

Literature searches of PubMed and Integrity (Thomson Reuters) for papers published through December 2014 were conducted with consideration of all alternative names of experimental pharmaceutical agents, including drug and chemical substances. To identify human randomized controlled studies, only "Human Studies" and "Randomized Controlled Trial" or "Clinical Trial" were considered.

Searches included articles that cited each eligible article to prevent potential oversight.

The following information was extracted for each eligible experimental pharmaceutical agent: development status (stage of clinical studies and general name of pharmaceutical agent) and first positive results for a randomized controlled trial (journal name, publication year, institute, industry involvement, and anticipated application). Searches were conducted in December 2014.

Outcomes

The primary outcome of interest was the time until translation to clinical application, which was defined as drug approval or publication of positive findings in randomized trials. If both outcomes occurred, the first to occur was defined as the primary outcome.

Statistical analysis

Kaplan-Meier curves were constructed for the time from publication to clinical application. Log rank test was conducted for comparison with the previous study [7]. Chi-square test was also conducted to compare backgrounds between articles resulting in clinical application and those not. Data were analyzed using JMP Pro 11 software (SAS Institute Inc., Cary, NC, USA). Significance level was less than 0.05.

Results

Of the 38,655 articles published from 1989 to 1993 in 8 major medical science journals, 1169 were selected based on key words. This number was then reduced to 202 after examination of abstracts and original articles (Figure 1).

None of these 202 articles were published in *Nature Biotechnology*, and only 1 was published in *Cell*. However, more articles were published in these journals in the latter half of the period covered in the previous study (from 1991 to 1993). More than half of the articles selected were animal studies, and approximately 70% focused on a specific technology. In the categories of promising technology, "Proteins, peptides, and amino acids" was the most extracted category, followed by "Substances" (Table 1).

Translation to clinical application

Of the 202 articles selected, 22 were eventually translated into clinical application, of which 21 were publications of positive randomized trials, 6 were drug approvals, and 5 were both. No marked differences were noted between articles that resulted in clinical application and those that did not with respect to background content, industry involvement, and categories of promising technologies. Significant differences were only noted in implications of promising technologies, with articles featuring implications for both therapy and prevention tending to advance to clinical application over those with no such implications (Table 2).

A total of 10.1% of examined articles were therefore eventually translated to clinical application, compared with the 19.8% (20 of 101 articles) reported in the previous study.

Period until clinical application

Mean period from publication until clinical application was 22.4 years in our study and 18.7 years in the previous study (Figure 2), a difference found to be significant using the log rank test ($p < 0.021$).

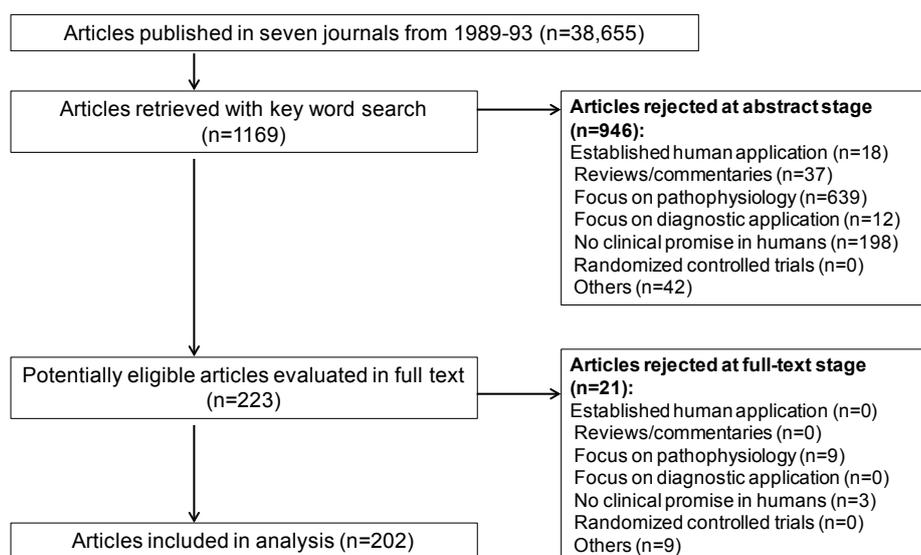


Figure 1. Selection of publications with promising therapeutic or preventive applications.

Figure 1 shows a selection process of publications with promising therapeutic or preventive applications. Of the 38,655 articles published from 1989 to 1993 in 8 major medical science journals, 1169 were selected based on key words. This number was then reduced to 202 after examination of abstracts and original articles.

Table 1. Characteristics of eligible publications.

	Number (n=202)
Journal	
<i>Nature</i>	14
<i>Cell</i>	1
<i>Science</i>	26
<i>Journal of Experimental Medicine</i>	18
<i>Journal of Clinical Investigation</i>	45
<i>Proceedings of the National Academy of Science</i>	92
<i>Nature Genetics</i>	6
<i>Nature Biotechnology</i>	0
Year	
1989	35
1990	38
1991	45
1992	43
1993	41
Industry involvement	
Author affiliation	68
Financial support without author	11
Provision of technology without author	7
None reported	116
Type of study	
Animal	122
Cellular	64
Human	13
Molecular	3
Category of promising technology	
Antibody	15
Cell	1
Protein/peptide/amino acid	60
Substance	49
Vaccine	34
Vector/gene/nucleic acid	43
Type of candidate technology	
Specific technology	138
Categories of technology	64

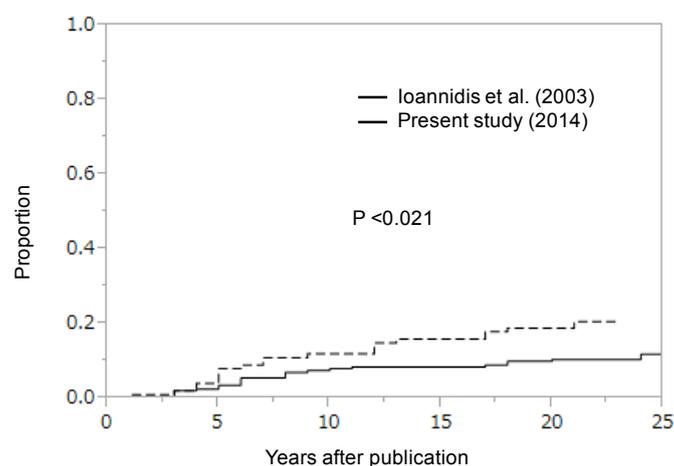


Figure 2. Proportion of candidate technologies translated to at least one positive randomized controlled trial or approval following initial publication.

Figure 2 shows Kaplan-Meier curves of proportion of candidate technologies translated to at least one positive randomized controlled trial or approval following initial publication. The dash line is the result of Ioannidis et al.'s study. The solid line is the result of present study. Mean period from publication until clinical application was 22.4 years in our study and 18.7 years in the previous study.

Discussion

Of the 202 articles identified through our literature search, only 22 were eventually translated into clinical application, with the mean period of time required until clinical application being 22.4 years—a duration significantly longer than that reported in the previous study. No marked differences were noted in background content between the articles that resulted in clinical application and those that did not, except for the implication of promising technologies. To our knowledge, this is the first comprehensive study to compare the clinical application of basic medical science research in the last decade.

Regarding the relationship between involvement of a pharmaceutical company and eventual clinical application, while some studies reported that funding by the pharmaceutical company was associated with positive findings in clinical trials [11–13], others

Table 2. Factors associated with clinical application.

	Positive RCT or Licensed/approved	Others	
Variable	% (n=22)	% (n=180)	
Industry Involvement			p=0.98
Author affiliation	36% (8)	33% (60)	
Financial support without author	5% (1)	6% (10)	
Provision of technology without author	57% (1)	58% (6)	
None reported	3% (12)	3% (104)	
Type of study			p=0.31
Animal	45% (10)	62% (112)	
Cellular	36%(8)	31% (56)	
Human	14% (3)	6% (10)	
Molecular	5% (1)	1% (2)	
Promising technology			p=0.27
Antibody	5% (1)	8% (14)	
Cell	0% (0)	1% (1)	
Protein/peptide/amino acid	45% (10)	28% (50)	
Substance	32% (7)	23% (42)	
Vaccine	14% (3)	17% (31)	
Vector/gene/nucleic acid	5% (1)	23% (42)	
Type of promising technology			p=0.32
Specific technology	59% (13)	69% (125)	
Categories of technology	41% (9)	31% (55)	
Implication			p=0.02
Therapeutic	73% (16)	80% (143)	
Preventive	14% (3)	18% (32)	
Therapeutic and preventive	14% (3)	2% (4)	
Target of potential application			p=0.73
1: Cancer	9% (2)	17% (30)	
2: Nerve	14% (3)	11% (20)	
3: Cardiology	0% (0)	3% (6)	
4: Metabolism/endocrine secretion	9% (2)	6% (10)	
5: Others	68% (15)	63% (114)	

reported no relationship [14,15]. Two articles included implications for their technology in both therapy and prevention for infectious disease [16,17], while one included implications for memory retention [18]. Research for pharmaceutical agents for both therapy and prevention might receive more funding than those for only therapy or prevention, possibly explaining why articles with implications for both tended to advance to clinical application.

In the present study, the proportion of reports reaching clinical application was lower and the period of time between publication and application longer than reported in the previous study. It was reported that the time until translation to clinical application varied according to the definition of clinical application [19]. However, our result was the same for decreasing of success rate of researcher who were funded by NIH R01 research grant [20]. This discrepancy might be due to emergence new categories of promising technologies. For example, in the previous study, "Substances" covered 70% of promising technologies in eligible basic science articles, followed by "Vaccines". In the present study, however, "Substances" covered only 24%, with an increasing percentage of new categories such as "proteins, peptides, and amino acids" and "vectors, genes, and nucleic acids". The proportion of "Substances" that advanced to clinical trials has remained consistent for the last 50 years [21]. These new categories might complicate the evaluation of subsequent clinical application.

Follow-up was 20 to 24 years in the previous study and 22 to 26 years in the present study. However, despite the longer follow-up, the proportion of reports reaching clinical application was lower and the time until application longer in the present study than in that conducted in 2003. The effect of these different follow-up periods might therefore be negligible. The number of patients in clinical trials has increased in recent years [22], and the number of clinical trials required for clinical approval is also increasing, along with the complexity of emerging treatments [22]. These problems might account for the prolonged time to clinical application.

A potential limitation to the present study warrants mention. Given that most research is published in English and our group is most familiar with Japanese, we only searched for articles written in these languages. Articles on randomized clinical trials published in languages other than English or Japanese journals may therefore have been missed. However, given that the majority of randomized clinical trials for promising pharmaceutical agents appear to have been published in English, this limitation may be negligible.

Zanamivir [23] and Abatacept [24] are blockbuster drugs developed through application of medical science research examined in the present study. However, research which led to the development of Sitagliptin, another blockbuster drug, was first published in *The Journal of Medical Chemistry* [25], which was not included in the present study. Basic medical science research resulting in clinical application might not be published exclusively in well-reputed journals.

Conclusions

We demonstrated that even in research published in major medical science journals, the prevalence of clinical application was lower and required more time than that reported 10 years prior. This finding suggests that research published in well-reputed journals does not always result in clinical application. Promising technologies should be carefully evaluated before study funds are allocated for the purpose of clinical application.

Authorship and contributors

NH has had the main responsibility for calculating statistics and writing the paper. KK is the principal investigator for the project, has planned the present paper jointly with NH, and has actively taken part in revising the paper. SS and YI have taken part in planning and analyzing data and revising paper.

Disclosure of potential conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this article and there has been no significant financial support for this work that could have influenced its outcome.

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