Treating patients with compounds or biological agents that pass the safety-test

There are numerous medical disorders without effective treatments. It is possible that many of un-treatable conditions need more than one compound co-operatively for improvement or cure. Approval of drugs in the U.S. is governed by a rigorous review process by the Food and Drug Administration (FDA) regulation. A sponsor must demonstrate the drug's safety and efficacy in well controlled clinical trials in the proper patient population for which it is indicated. Development of a new compound entity (NCE) is a very costly and time-consuming process; it takes roughly 15 years and 1.5 billion dollars on average. The high cost of the process makes the development of a new drug with multiple NCEs almost impossible. There are many compounds or biological agents which pass the safety test, but fail in the efficacy test. Those compounds might be critical for treatment of these medical conditions. The author suggests that compounds or biological agents, which pass the safety test, but the fail in efficacy test, should be allowed to use in clinical setting. The safety of those compounds is comparable with any other drugs approved by FDA. Benefits would heavily outweigh risks for patients treated by those compounds. The same principle should also be applied to biological agents, such as vaccines against HIV infection, cancers, etc.

PeerJ PrePrints | https://doi.org/10.7287/peerj.preprints.1626v1 | CC-BY 4.0 Open Access | rec: 5 Jan 2016, publ: 5 Jan 2016

Title: Treating Patients with Compounds or Biological Agents That Pass the Safety Tests

Author: Jianyi Zhang, MD/PhD

Affiliation: Self-employed physician

Corresponding author:

Jianyi Zhang: 900 S. Washington Street, Suite 112, Falls Church, VA 22046

jianyi.zhang66@gmail.com

PeerJ PrePrints | https://doi.org/10.7287/peerj.preprints.1626v1 | CC-BY 4.0 Open Access | rec: 5 Jan 2016, publ: 5 Jan 2016

Treating Patients with Compounds or Biological Agents That Pass Safety-Tests

Approval of drug products in the U.S. is governed by a rigorous review process conducted by the Food and Drug Administration (FDA). A sponsor must demonstrate the drug's safety and efficacy in well controlled clinical trials in the proper patient population for which it is indicated. The safety requirement for new drug products was established in the 1938 Federal Food, Drug and Cosmetic (FD&C) Act. A 1962 amendment to the FD&C Act additionally requires that a drug be shown to be effective through "substantial evidence" derived from "adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the involved" (Food, Drug and Cosmetic Act, Section 505.(d).).

Conceptually, according to drug treatment, diseases may be roughly divided into three types:

1. Diseases that can be treated effectively with a single drug

Some diseases can be cured with a single drug. For example, *Escherichia coli* causes urinary tract infections, *Staphylococcus aureus* can cause lobar pneumonia, and both of them used to be treated successfully with single antibiotics prior to the development of drug-resistant strains.

2. Diseases that can be treated effectively by different drugs separately and more effectively by a combination of different drugs

Different drugs may have a synergistic effect. Hypertension, diabetes, AIDS, asthma, and gastric ulcers belong to this category. There are eight categories of medications to treat hypertension; taking several drugs together can produce a stronger antihypertensive effect. Each drug in the cocktail recipes for AIDS treatment as well as gastric ulcers is an approved medication on the market.

3. Diseases that can only be effectively treated with different New Compound Entities (NCEs) together

An NCE approval to enter the market as a drug is called a Safety Passed & Efficacy Approved Drug (SPEAD). We can imagine another type of NCE that passes the safety test, but does not show efficacy in certain trials. This type of NCE might be essential or has the potential to play an important role in treatment of certain medications only if they are included in treatment with other potential beneficial compounds in the trial, which could be called Potential Therapeutic Drug (PTD). PTDs cannot pass the currently approved process into the market.

1. Jianyi Zhang is a physician in private practice in USA.

2. Correspondent: jianyi.zhang66@gmail.com

PeerJ PrePrints | https://doi.org/10.7287/peerj.preprints.1626v1 | CC-BY 4.0 Open Access | rec: 5 Jan 2016, publ: 5 Jan 2016

It is impossible to discern what disease falls into this category. We know that there are many severe, terminal conditions such as certain cancers, autoimmune diseases, and developmental disorders that currently have no effective treatments. Some of them might be well controlled or treated with two or more PTDs, or together with other drugs on the market, and they belong to the third type diseases.

In phase II trials, overall success rates were 28% (2006–2007), and 18% (2008–2009). Out of one reported failure, 51% (44 out of 87) were due to insufficient efficacy (Arrowsmith 2011). For every successful phase II trial, there are 2 trials that failed efficacy reasons. There were 83 phase III trials and submission failures between 2007 and 2010; failure rate is around 50%. Among those that failed, 66% are due to efficacy (Arrowsmith 2011). The failed NCEs might be used as PTDs for clinical applications.

Semagacestat, tramiprosate, tarenflurbil, and latrepirdine were high-profile, "would-be" Alzheimer's drugs that failed the last phase of clinical trials for efficacy reasons. Each made it through the safety stages, but failed efficacy tests (Rafii and Aisen 2009). They might be utilized in clinic as PTDs.

Phylogenetic reconstruction of primary renal carcinomas and associated metastatic sites revealed that 63 to 69% of all somatic mutations not detectable across every tumor region. Intratumor heterogeneity was observed for a mutation within an autoinhibitory domain of the mammalian target of rapamycin (mTOR) kinase (Gerlinger, Rowan et al. 2012).

Development of a new compound entity (NCE) is a very costly and time-consuming process; it takes roughly 15 years and 1.5 billion dollars on average. The high cost of the process makes the development of a new drug with multiple NCEs almost impossible.

It is unrealistic to expect one NCE to have desired effects on cancers that have enormous heterogeneity. However, the diseases might be better treated with several NCEs with or without combination with other drugs on the market.

Is there any way to deal with this third type of disease? A possible or partial solution to this dilemma is to let physicians use PTDs to treat medical conditions in clinical settings.

Any compound in the clinical trial is selected from thousand and thousand compounds with specific target. NCEs in the trials usually have different targets. Alzheimer's disease is a devastating neurological disorder that affects more than 37 million people worldwide. Synaptotoxic β-amyloid (Aβ) peptide, the plaques composed of aggregated Aβ, as well as the neurofibrillary tangles composed of hyperphosphorylated tau protein, are held to be essential to the pathogenesis of Alzheimer's disease (AD).

β-amyloid is a peptide of 39 to 43 amino acids. The isoforms with 40 and 42 amino acids (Aβ40/42) are the main constituents of amyloid plaques in the brains of Alzheimer's disease patients. β-amyloid is formed by proteolysis of APP.

Therapeutic strategies include blocking Aβ formation, slowing its aggregation into plaques, lowering its soluble levels in the brain, and disassembling pre-existing amyloid plaques.

Semagacestat is a γ -secretase inhibitor; which (along with β-secretase) is responsible for APP proteolysis (Fleisher, Raman et al. 2008). Tarenflurbil is a γ-secretase modulator (Eriksen, Sagi et al. 2003); tramiprosate directly binds Aβ to prevent Aβ aggregation (Gervais 2004). Even they were tested to be safe, but failed to show lack of efficacy in phase III studies, they might significantly improve medical condition of AD in the combination.

PTDs are compounds tested in trials in which safety is comparable with placebo or other SPEADs. Treating patients with them does not increase their risks compared with other drugs on the market.

There are a large number of PTDs and combinations of them are unlimited. PTDs are ineffective in the clinical trial separately, but may be effective when they are co-administered with other PTDs or approved drugs. Outcomes of their use might be one of four possibilities:

1) Combination is not secure and ineffective. The combination should not be used in clinical settings.

2） Combination is not safe, but effective. If so, the treating physician must weigh the risk to benefit ratio.

If the combination causes only nausea, vomiting and limb weakness but prolongs life, physicians might continue it. If patients have arrhythmia with the application, that combination should be disbanded.

3) Combination is safe, but ineffective. That is to say, the combination has no effect on the condition, and it should not be used in the treatment.

4) Combination is safe and effective. This is the ideal outcome.

By the FDA regulation, there is no PTD in the market, nor data to tell us what combination or in what circumstances is effective. With the PTD application, the doctor will soon discern the proper conditions to use PTDs, as well as what combination should not be used for certain conditions.

The clinical impacts of PTDs can be demonstrated in a few weeks or months, if not in a few days. The application might lead to remission of advanced cancer, improvement of autoimmune symptoms, neurologic recovery in stroke patients, and so on.

The cost of drug approval is in research and development. For each successful drug, pharmaceutical companies would have several PTDs locked in their safe boxes without any commercial interests. If a PTD can go onto the market for clinical use, it can provide major benefits for manufacturers.

Doctors will have many more options with PTDs. For each SPEAD in the market, there might be a few PTDs. Physicians might use these PTDs, or with combination with one or more SPEADs. The possibility of combinations is unlimited.

The targets of PTD treatment are serious medical conditions, such as Alzhemier's disease, cancers in terminal stage; these diseases have no treatments or ineffective ones at best. The application of PTD might effectively control and improve the condition, or even save lives.

The safety of PTDs is comparable with SPEAD; patients who take PTDs would bear no more risks compared with those who take SPEAD. Severe adverse with PTDs could be detected, controlled and eliminated in the practice with data available after clinical application. Benefits would heavily outweigh risks for patients that receive PTD.

Unlike SPEAD, the informed consent would be necessary prior to treatment and patients should know rationale of PTDs application, and proper monitoring system should be setup to check efficacy with combination among PTDs or PTD with SPEAD, beside severe side-effects, further clinical trial might be optional or necessary to verify the efficacy of PTDs after their usage.

Using PTDs in clinical settings is potentially a win-win-win situation for pharmaceutical companies, doctors, patients, and the governments.

The same principle should also be applied to biological agents, such as vaccines against HIV infection, cancers, etc.

There are many thousands patients dying, much more patients and their families suffering these medical conditions each days. Application of PTDs might save their lives and suffering.

Should we stick to the current process and expect a "miracle" NCE to be discovered to treat type III diseases? Or should we move a step forward to modify the currently available options to provide the patient a chance to survive and recover? Which way is more medically ethical? Which will keep the patient's best interests in mind? Is there any other way to treat the third type of diseases, if they exist or every likely exist?

Amendment to the current laws regarding the FDA regulation should be made which should allow clinical application of PTD in practice.

Embodiment 1:

Compounds A, B, C, D underwent phase III clinical trials individually in treatment of Alzheimer's disease, they were all demonstrated safe, but did not show efficacy for improvement of patients' cognitive functions.
These patients were prescribed these compounds with informed consent by different physicians, some of them take A and B, some A and C, some C and D. After 3 months many family members from the patients treated with C, D compounds reported that cognitive functions of their relatives in those medications significantly improved.

Later on, a random clinical trial was done in which C and D combination verse a placebo were included in the study. The result showed cognitive functions in the two groups were significantly different, the patients treated with some C and D compounds were much better than ones in the placebo group ($P<0.01$) in their cognitive functions, whereas there were no significant differences of side-effects among these two groups.

Embodiment 2:

Compounds X, Y, Z underwent phase III clinical trials individually in treatment of prostate cancer, they were all demonstrated safe, but did not show effective to reduce the tumor size. These patients were prescribed these compounds with informed consent by different physicians, some of them take X plus medication alpha in the market (the first group), some take Y plus medication alpha (the 2nd group), and some take Z plus medication alpha (the 3rd group). Information were collected in central office. Data analysis shows tumor size in the 1st group patients shrinked tremendously, whereas tumor size in other two groups did not have significant change.

A random clinical trial was done in which the first group are compared with these other two groups. The result showed that tumor in the first group was almost un-detectible, whereas the sizes in other groups placebo group had no apparent changes.

Embodiment 3:

Vaccines M, N underwent phase III clinical trials individually for prevention of HIV infection, they were all demonstrated safe, but did not show efficacy to reduce HIV infection.

Vaccines M, N were given to all self-claimed homosexual men in area A, incidence of HIV infection was found to decrease 80% from the previous year among these patients compared with ones who did not receive these vaccines in the area.

A random clinical trial was done in which the first group of patients receive vaccines M, N; the 2nd group of patient received only vaccines M, the 3rd on received placebo. Each group has 1,000 persons.

After one year, it is found that nobody in the first group with HIV infection; 2.1 % persons with HIV + in the 2nd group, and 2.5 % persons HIV + in the placebo group.

References

Arrowsmith, J. (2011). "Trial watch: Phase II failures: 2008-2010." Nat Rev Drug Discov **10**(5): 328-329.

Arrowsmith, J. (2011). "Trial watch: phase III and submission failures: 2007-2010." Nat Rev Drug Discov **10**(2): 87.

Eriksen, J. L., S. A. Sagi, et al. (2003). "NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo." J Clin Invest **112**(3): 440-449.

Fleisher, A. S., R. Raman, et al. (2008). "Phase 2 safety trial targeting amyloid beta production with a gamma-secretase inhibitor in Alzheimer disease." Arch Neurol **65**(8): 1031-1038.

Gerlinger, M., A. J. Rowan, et al. (2012). "Intratumor heterogeneity and branched evolution revealed by multiregion sequencing." N Engl J Med **366**(10): 883-892.

Gervais, F. (2004). "Gag mimetics: potential to modify underlying disease process in AD." Neurobiol. Aging **25**: S11-12.

Rafii, M. S. and P. S. Aisen (2009). "Recent developments in Alzheimer's disease therapeutics." BMC Med **7**: 7.