PREDICTION OF NOVEL THERAPEUTIC INDICATION FOR ROSIGLITAZONE USING ITS REPORTED CLINICAL SIDE-EFFECTS: DRUG REPOSITIONING BY PHARMACOVIGILANCE APPROACH

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ABSTRACT

Drug repositioning by Pharmacovigilance approach is primary objective of this study. We consider rosiglitazone as target molecule for this pilot scale study. Rosiglitazone is an anti-diabetic drug of thiazolidinedione class. It works as an insulin sensitizer, by binding to the peroxisome proliferator activated receptor (PPAR) gamma in fat cells and making the cells more responsive to insulin. Rosiglitazone has been selected as target molecule because most recently on 16 December 2015 in interest of its safety, United States Food and Drug Administration (USFDA) announced to eliminate the risk evaluation mitigation strategy for rosiglitazone and confirmed it as one of the safe and effective treatment for diabetes. For this study we retrieved total 6,884 adverse drug reaction cases of rosiglitazone from drug safety database of USFDA covering the duration from 2010 to 2015. With respect to our study objective, we analysed 5,844 cases of rosiglitazone reported with non-serious side effects thoroughly using its phenotypic parameters (pharmacologic mechanism of action and safety) and proposed two novel therapeutic indications for rosiglitazone use either in Alzheimer’s disease or in hypertension. Further studies covering the data for larger duration and same objective may adjuvant our results for the reposition of rosiglitazone by Pharmacovigilance approach.

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1. INTRODUCTION
Drug repositioning is the novel concept to identify the new indications for drugs which are already approved and marketed for the treatment of unintended diseases. The traditional approach for drug development is a time-consuming and very expensive process. By approximate, it now takes at least 12 to 15 years and $500 million to $2 billion to bring a single pipeline molecule to the market.\[1\] Though, companies spend much on drug development process, the number of new molecules approved by the regulatory authorities has been declining since last two decades. Lack of efficacy and adverse side-effects are two major causes for which a drug fails in phase II and phase III clinical trials.\[2\] Hence the development of novel concept which could predict new therapeutic indications holds great promise to increase the efficiency of block buster molecules of any pharmaceutical organization and to improve the drug discovery pathway.

Initiation of drug repositioning for known molecules with well characterized safety and efficacy profiles could help us to identify the new therapeutic indication for unintended disease and its better transition for respective population. There are few examples for successful serendipitous drug repositioning as following: (1) thalidomide for the treatment of leprosy and (2) finasteride for the prevention of baldness. The transition of sildenafil for treatment of erectile dysfunctions is one of the best example for drug repositioning. In 1980, Pfizer Inc. had invented sildenafil for the treatment of coronary artery disease which acts through inhibition of phosphodiesterase type 5. Penile erection for longer duration was identified as one of its side-effect during the Phase I clinical trials with the patients of hypertension and angina pectoris.\[3\] Sildenafil was not found so efficacious for the treatment of angina pectoris in few small scale clinical trials and later it has been approved/repositioned in 1998 by USFDA for the treatment of erectile dysfunction.

Discoveries about the molecular basis of disease provide unprecedented opportunities to translate research findings into new medicines. However, developing a brand-new drug takes an enormous amount of time, money and effort, mainly due to bottlenecks in the therapeutic development process. Delays and barriers mean that translation of a promising molecule into an approved drug often takes more than 14 years. It is crucial to advance strategies to reduce this time frame, decrease costs and improve success rates. Drug repurposing is one such
strategy. Many agents approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. Because repurposing builds upon previous research and development efforts, new candidate therapies could be ready for clinical trials quickly, speeding their review by the Food and Drug Administration and, if approved, their integration into health care. In general, the drug repositioning approach we used in this study is deals with the observational data of human being which is reported by different pharmaceutical organizations or healthcare professionals to FDA Adverse Event Reporting System (AERS) during their routine pharmacovigilance activity. This clinically proved data used for drug transition for the treatment of unintended disease will be more reliable in terms of efficacy and cost effectiveness. Another reason why drug repositioning may be one of the efficient approach for drug discovery is because post-marketed drugs are already proved for its (1) Chemistry, Manufacturing and Control profile, (2) well versed pharmacokinetic and pharmacodynamic profile\(^4\) and (3) better safety and efficacy profile.\(^5\)

2. MATERIAL AND METHOD

Pharmacological data were collected from FDA Adverse Event Reporting System (FAERS) covering six years duration from 2010 to 2015. In our study, patient receiving treatment with either anti-diabetic drugs or drugs acting on cardio vascular system was only selected as inclusion criteria for further analysis. Patients reported with serious adverse events were excluded from the further analysis. Primary analysis was performed for reported source data including study variables as patient demographic details, past medical history, current medical condition, concurrent drug therapy, and reported non-serious adverse event. As per the study objective, considering primary analysis of source data; rosiglitazone was selected as drug of choice for its reposition in unintended indication. Rosiglitazone is an anti-diabetic drug from thiazolidinedione class. It works as an insulin sensitizer, by binding to the peroxisome proliferator-activated receptor (PPAR) gamma in fat cells and making the cells more responsive to insulin. Medical dictionary for Regulatory Activities (MedDRA Version 19.1) was used to retrieve the relevant MedDRA preferred terms for reported non-serious side-effects of rosiglitazone.

Statistical analysis was performed by calculating the proportional reporting ratio (PRR) and chi-square value for all the reported non-serious adverse events with rosiglitazone which were considered to have minimum correlation with proposed novel therapeutic indication for
rosiglitazone. Study outcome was supposed to be considered as positive, if value of calculated PRR reports $\geq 2$ and value of Chi-square reports $\geq 4$.

\[
\begin{align*}
\text{Proportional Reporting Ratio (PRR)} & = \frac{A}{(A+B)/(C/(C+D))} \\
\text{Chi-square} & = \frac{(AD-BC)^2}{(A+B+C+D)/[(A+B)(C+D)(A+C)(B+D)]}
\end{align*}
\]

Study approach includes identifying the new indication of drugs for unintended disease based on their reported side effects. If two drugs for the treatment of different disease are causing similar side effects, then it indicate that there may be a possible correlation in between two drugs for some common mechanism of action and target receptor site. In other words, there is a phenotypic co-relation between side effect and disease. Cases reported with only non-serious side effects for at-least 3 times with same drug were only considered for objective analysis.

3. RESULT
Total 6,884 cases were retrieved from FDA-AERS for rosiglitazone covering the duration from 2010 to 2015. From the above cases, 1040 cases were reported with at-least one serious side effect and hence they were excluded from the further analysis. Remaining 5,844 cases were reported with non-serious side effects. These non-serious cases were further analysed for its reported side-effects, its reporting pattern in individual age group and reporting frequency. Most common reported side effects were weight increased (n=571, 10%), depression (n=542, 9%), amnesia (n=429, 7%), anxiety (n=429, 7%), blood glucose increased (n=255, 4.2%), pleural effusion (n=247, 4.1%), mild convulsion (n=226, 4%), heart rate increased (n=187, 3.1%) and insomnia (n=158, 3%).

Of these all non-serious reported events; depression, anxiety and mild convulsion events were integrated with rosiglitazone pharmacologic characteristics (mechanism of action and safety profile) and diseases to predict novel therapeutic indication. These hypothetical data are summarized below in the Table 1 and statistical analysis is depicted in Table 2:.
Table 1: Rosiglitazone - Reported Side Effects, Proposed Novel Therapeutic Indication and Mechanism of Action.

<table>
<thead>
<tr>
<th>Reported Side-effects (SEs) of Rosiglitazone</th>
<th>Total No. of SEs</th>
<th>New role of rosiglitazone for the treatment of unintended disease to identify the novel therapeutic indication</th>
<th>Proposed Novel Therapeutic Indication</th>
<th>Proposed Cellular Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, Anxiety, Mild convulsion</td>
<td>N = 1197</td>
<td>Rosiglitazone has an unintended effect on central nervous system through altering the brain insulin and glucose utilization affecting circulating concentrations of glucose, insulin, inflammatory markers, and by generation of reactive oxygen species. Insulin has an important role in normal brain functioning, and insulin-signalling dysfunction is increasingly recognized for its association with Alzheimer’s disease (AD) in preclinical and comparative post-mortem neuropathology studies. These discoveries have given way to a growing interest in restoring insulin signalling in AD with therapeutic agents originally developed for the treatment of T2DM.</td>
<td>In mild to moderate Alzheimer's disease it may improve the cognitive functions&lt;sup&gt;[6-9]&lt;/sup&gt;</td>
<td>(1) Rosiglitazone may affect the beta amyloid formation by inhibition of beta-secretase enzyme or; (2) Prevent tau protein to convert into a tangles or; (3) Altering the peripheral insulin and central nervous system glucose utilization or; (4) Increase hippocampal glucose transporter expression</td>
</tr>
<tr>
<td>Depression</td>
<td>N = 542</td>
<td>Published studies shows that people with diabetes have a greater risk of depression. Considering that, over here depression is not a side-effect reported by rosiglitazone. It has been considered as one of the common risk of diabetes. Treatment with rosiglitazone causes decrease in hyperinsulinemia which indirectly causes down-regulation of renal dopamine receptor (type D1) function. Dopamine, by activating D&lt;sub&gt;1A&lt;/sub&gt; receptors, inhibits sodium transporters (Na,K-ATPase and Na,H-exchanger) in renal proximal tubules and promotes sodium and water excretion.</td>
<td>In mild to moderate hypertension&lt;sup&gt;[10-14]&lt;/sup&gt;</td>
<td>Rosiglitazone may restore the renal dopamine (D1) receptor. Dopamine receptors are linked to phospholipase C and adenylyl cyclase, by coupling with G-protein couple receptor channel. The activation of dopamine receptors and succeeding stimulation of second-messenger pathways lead to the inhibition of sodium transporters - Na/H-exchanger (NHE) and Na/K-ATPase (NKA) and thereby an increase in renal sodium excretion and reduction in blood pressure.</td>
</tr>
</tbody>
</table>
Table 2: Statistical Signal Analysis.

<table>
<thead>
<tr>
<th>Events (R)</th>
<th>Medicinal Product (P = Rosiglitazone)</th>
<th>All other medicinal products</th>
<th>PRR</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A+B</td>
<td>C</td>
</tr>
<tr>
<td>Depression</td>
<td>542</td>
<td>2,302</td>
<td>2,844</td>
<td>4,952</td>
</tr>
<tr>
<td>Anxiety</td>
<td>429</td>
<td>2,415</td>
<td>2,844</td>
<td>5,262</td>
</tr>
<tr>
<td>Convulsion</td>
<td>226</td>
<td>2,618</td>
<td>2,844</td>
<td>2,300</td>
</tr>
</tbody>
</table>

A = number of individual cases with the suspect medicinal product P involving an adverse event R.
B = number of individual cases related to the suspect medicinal product P, involving any other adverse event except R.
C = number of individual cases involving event R in relation to any other medicinal products but P.
D = number of individual cases involving any other adverse events except R and any other medicinal products except P.

4. DISCUSSION

In this study based on the commonly reported side-effects of rosiglitazone, we proposed two novel therapeutic indications for (1) Alzheimer’s disease, and (2) Hypertension. They are discussed below in details.

4.1 Rosiglitazone in Alzheimer’s disease

Through exhaustive literature search it has been identified that Alzheimer disease and diabetes mellitus-type 2 are two of the most prevailing diseases world-wide. As per the announcement from Alzheimer’s Association in 2016, an approximate 5.4 million people of all ages in America have Alzheimer’s disease.[16] Thiazolidinediones are PPARγ agonist, which can inhibit β-secretase enzyme and thus increase the degradation of β-amyloid which is one of the main risk factor for occurrence of Alzheimer disease. In past few large phase 2/3 studies (REFLECT-4 and REFLECT-5 trials of innovator -GlaxoSmithKline) of Avandia® (rosiglitazone) were initiated for confirmation of its safety and efficacy in Alzheimer disease. However those studies have been discontinued because of its cardiovascular risk reported in a meta-analysis.[17] However, in December 2015, USFDA has announced that, there is no direct causal relationship of rosiglitazone for cardiovascular risk reported previously. It has been confirmed by USFDA that rosiglitazone is one of the safe
and effective treatment for diabetes. GlaxoSmithKline has recently been completed the Study AVA104617 with an objective to evaluate the long-term safety and tolerability of rosiglitazone in subjects with mild to moderate Alzheimer's disease. There was a mean decline of 4.5 points on mini mental state examination (MMSE) at week 48 from the baseline of open-label study. Due to non-randomized study design, efficacy result of this study can only be considered exploratory. The another preliminary study had concluded that rosiglitazone 4 mg/day may enhance the memory and intensify the attention power.[18]

4.2 Rosiglitazone in Hypertension

Epidemiologic data suggest 45-50% of prevalence rate for hypertension in diabetes patient. Published literatures suggest that rosiglitazone has efficacious effect on elevated blood pressure along with its mechanism as insulin resistance.[13, 19] The result of one recent interventional clinical trial for evaluation of cardiac output and glucose regulation in diabetes patient showing that approximate 80% (668 of 759 patient) of the patients treated with rosiglitazone were having more efficacious effect for lowering of blood pressure in compared with other anti-diabetic treatment like metformin and sulphonylurea.[20] In another study,[21] it shows that treatment with rosiglitazone in hypertensive patient for approximate 8 months can reduce systolic/diastolic blood pressure from 1.3 to 2 mmHg more effectively in compared with glibenclamide and hence further it may reduce occurrence of subsequent cardiovascular events.[22,23]

In the interests of rosiglitazone safety, on 16 December 2015 - USFDA has announced that marketing of rosiglitazone will not be hindered that was obstructed in 2010. FDA has re-evaluated the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) trial and confirmed that there is no direct causal relationship between rosiglitazone and increase risk of cardio vascular disease. Moreover for rosiglitazone, FDA has also eliminated the risk evaluation and mitigation strategy for rosiglitazone.[24]

Further research on effectiveness of rosiglitazone in larger population of Alzheimer's disease and hypertension may helpful to provide a better conclusive drug-reposition.

5. CONCLUSION

Through this research article, hereby we predict an opportunity for novel therapeutic indication of rosiglitazone use for the treatment of Alzheimer’s disease and hypertension with
an emphasis on next-generation phenotypic approaches of research for new molecular entity, which may provide a promising result outcome.

Overall in last 10-15 years, few pharmaceutical organizations have established a separate drug-repositioning department in their research units which is known as drug discovery unit or novel therapeutic indication unit. These organizations have successfully launched their multiple approved molecules for unintended indications through a path of drug-repositioning and got the health regulatory approvals with minimum cost of development.

Though there is a very low chance to challenge new potential therapeutic indications of few blockbuster molecules for an orphan disease through drug-repositioning pathway, it may enhance the fiscal growth of the organization globally and could keep the intellectual property rights or patent alive for an innovator organization with a single successful transition.

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Conflict of Interest: None.

REFERENCES


