The Risk of Hyperglycaemia with the use of Rituximab in Rheumatoid Arthritis. Results from a Meta-analysis of Randomised Clinical Trials

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## Authors:

<table>
<thead>
<tr>
<th>Author</th>
<th>Current affiliation</th>
<th>Conflict of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luis Velez-Nandayapa</td>
<td>1 and 2</td>
<td>2 and 4</td>
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<tr>
<td>Laura DeVore</td>
<td>3</td>
<td>2 and 4</td>
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<tr>
<td>Chahna Parikh</td>
<td>2</td>
<td>2 and 4</td>
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</table>

1. PhD candidate at the Pharmacoepidemiology Unit of Basel, University of Basel
2. MSc candidate at the University of Portsmouth and the Drug Safety Research Unit
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Agenda

- Hyperglycemia as a risk
- Background Rituximab (RTX) and hyperglycemia
- The systematic review
- The meta-analysis
- Results
Drug-induced hyperglycaemia (DIH) is often benign and most of the times, clinically asymptomatic [1-4].

Diabetic ketoacidosis and hyperglycemic coma may occur (severe manifestations DIH) [1-4].

Exact incidence of DIH in general is unknown; however, meta-analysis have estimated the incidence of DIH in glucocorticoids and immunosuppressive agents [2, 3].

Drugs may induce hyperglycaemia through a variety of mechanisms [1].

FDA in March 2004 requested a warning be added to the prescribing information for all atypical antipsychotics regarding the risk of hyperglycemia and diabetes [1].
Mechanisms of DIH & drugs implicated

Diminution of insulin secretion and/or insulin production
- Beta antagonists\(^a\) (effects are attenuated but not abolished with cardioselective drugs)
- Calcium-channel antagonists (related to calcium-channel blockade)
- Phenytoin
- Pentamidine\(^a\)
- L-asparaginase
- Imunosuppressive drugs (tacrolimus, cyclosporine)
- Diazoxide (direct effect on potassium channels)
- Diuretics (related to hypokalaemia)
- Antiarrhythmics\(^a\)

Diminution of peripheral insulin sensitivity and/or promotion of weight gain
- Atypical antipsychotics
- Antidepressant drugs
- Glucocorticoids\(^a\)
- Beta agonists\(^a\)
- Oral contraceptives

Protease inhibitors
- Growth hormone
- Nicotinic acid\(^a\)
- Nucleoside reverse transcriptase inhibitors (except for didanosine)
- Diuretics\(^a\)
- Statins\(^a\)
- Interferons\(^a\)

Increase in glucose production through promotion of hepatic gluconeogenesis and/or glycogenolysis
- Glucocorticoids\(^a\)
- Nicotinic acid\(^a\)
- Beta antagonists\(^a\)
- Diuretics\(^a\)
- Beta agonists\(^a\)

Destruction of pancreatic cells, leading to beta-cell injury
- Didanosine
- Interferons\(^a\)
- Pentamidine\(^a\)
- Statins\(^a\)
- Glucocorticoids\(^a\)

\(^a\) More than one mechanism is proposed

Background RTX

- RTX is an anti-CD20 monoclonal antibody
- Indications: Non-Hodgkin’s lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), and Rheumatoid arthritis (RA) in comb MTX.
- In animal models RTX induced hyperglycaemia (CD20 transgenic non-obese-diabetic mouse models).
- The association of hyperglycemia and RTX in patients with hematologic and solid tumors has been clearly confirmed [5].
- Hyperglycemia in hematologic malignancies has been associated with poor outcomes including increased risk of infection, organ dysfunction, durability of remission, graft-versus-host disease, and mortality [6,7].
Mechanism of Action

Apoptosis

MAC

ADCT

Opsonisation/phagocytosis
Our protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (reg. no. CRD42015015655).

We followed (development protocol and project) ...

- The PRISMA Statement
- The Cochrane Handbook
- and the Cochrane Adverse Effects Methods Group
The systematic review and Meta-analysis

• Search strategy: involved randomised CTs using RTX in RA, and it was performed from January 1990 to December 2015 in Medline, EMBASE and Cochrane Library databases.

• Outcomes evaluated: were the number of AEs and hyperglycaemia reported as outcomes of interest.

• Analysis of odds ratio (OR) as measure of effect and 95% confidence intervals (CI95%) and p-values as generated from the $x^2$ /Fisher’s exact test were calculated; heterogeneity was assessed using the $I^2$ test.

• Model: random effects models.

• Software used: CMA and Endnote
Results

- Search retrieval: 893 hits
- After removal of duplications and other topics nine publications matched our inclusion and exclusion criteria involving 2,997 subjects of which two publications were included in the meta-analysis involving 322 subjects.
- Outcomes reviewed: 110 different PTs
- I will show you the results of ONE outcome - hyperglycemia
## Results

<table>
<thead>
<tr>
<th>Ref</th>
<th>Author</th>
<th>RTX</th>
<th>RTX+MTX</th>
<th>RTX+CFM</th>
<th>PLC+MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tak PP, 2012</td>
<td></td>
<td>499</td>
<td></td>
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<tr>
<td>2</td>
<td>Rubbert-Roth A, 2010</td>
<td></td>
<td>343</td>
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<td>3</td>
<td>Greenwald MW, 2011</td>
<td>33</td>
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<td>4</td>
<td>Emery P, 2006</td>
<td>337</td>
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<td>5</td>
<td>Mease PJ, 2008</td>
<td>320</td>
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<td>155</td>
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<td>6</td>
<td>Cohen SB, 2006</td>
<td>309</td>
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<td>7</td>
<td>Emery P, 2010</td>
<td>316</td>
<td></td>
<td>149</td>
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<tr>
<td>8,9</td>
<td>Edwards+Keystone, 2012</td>
<td>40</td>
<td>40</td>
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</table>

Total: 40 2,197 41 719
## Results

<table>
<thead>
<tr>
<th>Group (cases/controls)</th>
<th>OR</th>
<th>95%CI</th>
<th>$p$-value $\chi^2$</th>
<th>$p$-value Fisher’s*</th>
<th>$I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTX (2/38) vs PLC-MTX (3/37)</td>
<td>0.64</td>
<td>0.05-6.04</td>
<td>0.6442</td>
<td>0.5000</td>
<td>0.000</td>
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<tr>
<td>RTX-MTX (3/37) vs PLC-MTX (3/37)</td>
<td>1.00</td>
<td>0.19-5.28</td>
<td>1.000</td>
<td>0.6624</td>
<td>0.000</td>
</tr>
<tr>
<td>RTX-CFM (3/38) vs PLC-MTX (3/37)</td>
<td>0.97</td>
<td>0.19-5.14</td>
<td>0.975</td>
<td>0.6504</td>
<td>0.000</td>
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</table>

RTX  rituximab  
MTX  methotrexate  
PLC  placebo  
CFM  cyclophosphamide

* Fisher’s exact test
Conclusion

• Our results suggest no evidence of association between rituximab in RA and the risk of hyperglycaemia, but the possibility of type II error is likely due to the fact that only two publications, using the same sample, reported the outcome of hyperglycaemia with a frequency between 5 to 7.5%. Further studies are needed to confirm/reject our findings.

Note

In 2010, the CONSORT Statement, (Consolidated Standards of Reporting Trials) was published, which provides the recommendations for better reporting of harms.

In 2007, the International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP) provided recommendations/guidelines for better reporting of published case reports.
Strengths and limitations

Strengths of the study

• The major strength of this review is the systematic approach for selection of studies and the performance of the varied meta-analyses for safety outcomes, with strict adherence to the PRISMA-Protocol 2015 Statement, the PRISMA Statement, the Cochrane Handbook and the Cochrane Adverse Effects Methods Group.

Limitations of the study

• The most important limitation is the fact that only one study (TWO studies with same sample) report hyperglycemia as safety outcome (reporting bias). More comprehensive reporting would have an important impact in the effect size for hyperglycemia.


Thank you
For your attention

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