BACKGROUND

- While immune checkpoint inhibitors (ICI) are important additions to the armamentarium in the fight against advanced renal cell carcinoma (aRCC), ICIs are associated with significant endocrine toxicities.
- We conducted a systematic review and meta-analysis of phase 3 randomized controlled trials (RCTs) to determine the risk of various endocrinopathies associated with first-line use of ICIs-based regimens for the treatment of aRCC.

METHODS

- Literature search: We systematically conducted a comprehensive literature search using PUBMED, Web of Science, EMBASE databases, and meeting abstracts from inception through May 2019.
- All databases and meeting abstracts were systematically searched with the keywords: 'Immune Checkpoint Inhibitors', 'Immunotherapy', 'Ipilimumab', 'Nivolumab', 'Atezolizumab', 'Avelumab', 'Pembrolizumab', and 'Renal Cell Cancer'.
- We limited our search to 'human', 'English language', and 'randomized controlled trials'.
- Eligibility criteria: Phase 3 RCTs using ICIs in the intervention arm for the first-line treatment of advanced renal cell carcinoma (aRCC), ICIs are associated with significant endocrinopathies. For eligibility each study was screened by at least two authors. Two authors conducted the data synthesis and analysis.

RESULTS

- For hyperthyroidism and adrenal insufficiency, three RCTs — CheckMate 214, IMmotion151, and JAVELIN Renal 101 — were analyzed. For hypothyroidism, all four RCTs randomizing 3706 patients were analyzed.
- For hypothyroidism and adrenal insufficiency, three RCTs — CheckMate 214, IMmotion151, and KEYNOTE-426 — were analyzed.
- The incidence of adrenal insufficiency in ICI-based regimens vs sunitinib are as follows — hypothyroidism: 3.36% vs 0.07%; hypophysitis: 2.76% vs 0%; and diabetes 0.7% vs 0%.
- The pooled RR of any grade endocrinopathies are as follows — hypothyroidism: 3.28 (95% CI: 2.26 - 4.75, P < 0.00001, I² = 19%); adrenal insufficiency: 19.52 (95% CI: 4.70 - 81.07, P < 0.0001, I² = 0%); hypophysitis: 2.76 (95% CI: 1.63 - 4.62, P < 0.001, I² = 69%); and diabetes: 4.44 (95% CI: 0.82 - 21.83, P = 0.08, I² = 69%).

CONCLUSIONS

- The relative risk of hypothyroidism, adrenal insufficiency and hypophysitis was significantly higher with immune checkpoint inhibitor based regimens compared to sunitinib for the treatment of advanced renal cell carcinoma.
- Although hypophysitis was the most commonly reported endocrinopathy in all the trials, the relative risk of hypophysitis was significantly higher in immune checkpoint inhibitor arms compared to sunitinib arms.
- A careful monitoring of the endocrine functions and initiation of appropriate treatment is crucial to reduce endocrine related morbidity and mortality in these patients.

REFERENCES


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Table 1. Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Phase</th>
<th>Type</th>
<th>Cancer</th>
<th>Line of treatment</th>
<th>Regimen Used</th>
<th>Total Efficacy</th>
<th>Total Safety</th>
<th>Total Risk Ratio</th>
<th>Pooled RR (95% CI)</th>
<th>Pooled RR (95% CI)</th>
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<tbody>
<tr>
<td>IMmotion151</td>
<td>RCT III</td>
<td>aRCC First-line</td>
<td>phase 3</td>
<td>Renal Cell Cancer</td>
<td>Nivolumab and Atezolizumab</td>
<td>3,501</td>
<td>1,672</td>
<td>1,829</td>
<td>0.91 (0.83 - 1.00)</td>
<td>1.00 (0.68 - 1.49)</td>
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<tr>
<td>CheckMate 214</td>
<td>RCT III</td>
<td>aRCC First-line</td>
<td>phase 3</td>
<td>Renal Cell Cancer</td>
<td>Nivolumab</td>
<td>1,307</td>
<td>796</td>
<td>511</td>
<td>0.75 (0.65 - 0.88)</td>
<td>1.00 (0.68 - 1.49)</td>
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<tr>
<td>KEYNOTE-426</td>
<td>RCT III</td>
<td>aRCC First-line</td>
<td>phase 3</td>
<td>Renal Cell Cancer</td>
<td>Atezolizumab and Bevacizumab</td>
<td>451</td>
<td>446</td>
<td>1</td>
<td>1.00 (0.68 - 1.50)</td>
<td>1.00 (0.68 - 1.50)</td>
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<tr>
<td>JAVELIN Renal 101</td>
<td>RCT II</td>
<td>aRCC First-line</td>
<td>phase 2</td>
<td>Renal Cell Cancer</td>
<td>Atezolizumab</td>
<td>413</td>
<td>413</td>
<td>1</td>
<td>1.00 (0.68 - 1.50)</td>
<td>1.00 (0.68 - 1.50)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Flow diagram of the study selection process.

Fig. 2. Pooled RR for any-grade hypothyroidism associated with immune checkpoint inhibitor-based regimens.

Fig. 3. Pooled RR for any-grade adrenal insufficiency associated with immune checkpoint inhibitor-based regimens.

Fig. 4. Pooled RR for any-grade diabetes associated with immune checkpoint inhibitor-based regimens.

Fig. 5. Pooled RR for any-grade hypophysitis associated with immune checkpoint inhibitor-based regimens.

Fig. 6. Pooled RR for any-grade adrenal insufficiency associated with immune checkpoint inhibitor-based regimens.