Can we predict relapse in Graves’ disease? Results from a Systematic Review and Meta-analysis

Appendix

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Study Protocol for Systematic Review of Graves’ disease

Risk factors predicting recurrence of hyperthyroidism after antithyroid drug treatment in Graves' disease: a systematic review and meta-analysis of retrospective, (non-) randomized, and observational trials

Rationale for Review

Up to date most patients in Europe and Asia are firstly treated for 12 to 18 months with ATD without an assessment of risk factors of relapse. Our aim is a stratification of treatment strategy for every patient according to his personal risk factors before treatment, thus facilitating the planning of further interventional studies.

Objective following PICOS

Population: non pregnant female and male patients with Graves’ disease (low TSH, high fT4, positive TRAB) older than 16 years; Intervention: under initial therapy with thyreostatic drugs during first episode; Comparator: no comparator, addition of T4 or T3 allowed; Primary Outcome: risk score of relapse based on pretreatment risk factors; Secondary outcomes: none; Study design: RCT, observational and retrospective cohort studies

Keywords and Strategy of Search
Databases

Embase (End of July 2015); Pubmed (End of July 2015); CENTRAL Cochrane Library (End of July 2015).

Additionally, cross referencing of similar literature (i.e. preexisting systematic reviews).

PUBMED: (graves OR basedow) AND (recurrence OR relapse) n=1176
EMBASE: graves AND ('relapse'/exp OR relapse OR 'recurrence'/exp OR recurrence) n=1604
CENTRAL: Search all text, only trials: (graves OR basedow) AND (recurrence OR relapse) n =94

Inclusion criteria

− human studies with adult patients with first episode of Graves’ disease receiving medical treatment
− no language restriction
− no restrictions in publishing status or type of literature
− observational, retrospective and prospective trials

Exclusion criteria

− pregnancy
− case reports
− follow up <12 months
− ATD treatment <12 months
− Solely on ophthalmopathy/orbitopathy
− radio iodine therapy
− thyroidectomy
− no reporting of pretreatment risk factors
Remission after second ATD course or no remission at all (to be categorized as treatment failures)

**Study selection**

Eligibility assessment is being performed by two unblinded reviewers, and disagreements are resolved by assessment through a third reviewer. No kappa statistic for reviewer agreement, but disagreements will be discussed in text.

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<tr>
<th>Reasons for 1. step of exclusion (title and abstract)</th>
<th>Numbers</th>
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<tr>
<td>Not meeting inclusion criteria/different subject</td>
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<td>Animal study</td>
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<td>Case report/correspondence/review</td>
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<td>Children &lt;16y or pregnancy</td>
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<td>Only orbitopathy/ophthalmopathy</td>
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<th>Reasons for 2. step of exclusion (full text)</th>
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<tr>
<td>follow up &lt;12 months</td>
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<td>No included intervention (only ophthalmopathy/orbitopathy without data on thyroid etc)</td>
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<tr>
<td>No RCT, retrospective or observational study</td>
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Insufficient data (not reporting selected outcome, etc.)

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<th>No individual data</th>
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<td>Irretrievable</td>
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Data was extracted by a single reviewer. For assessing the risk of bias we used SIGN system. We also consulted the Cochrane Handbook for Systematic Reviews of Interventions. The sheets/tables were created a priori.

**Statistical analysis**

Alpha level of 5%. Use of STATA and the user written commands on meta-analysis/regression (metan and metareg). Funnel plot for bias across studies and if in doubt an Egger’s test. Use of random effects model. Sensitivity and subgroup analysis as possible on available data (not restricted).