Statistical Analyses Plan

Acupuncture for Seasonal Allergic Rhinitis (ACUSAR) – A Randomised Controlled Trial

Acupuncture for Seasonal Allergic Rhinitis (ACUSAR) – A Randomised Controlled Trial

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Version – May 7, 2010
Contents

1. Objectives/Hypotheses .............................................................................................................. 1
2. Design .......................................................................................................................................... 1
3. Populations for analyses ........................................................................................................... 2
   3.1. Intention to treat Population .............................................................................................. 2
   3.2. Per protocol Population ...................................................................................................... 2
4. Variables and endpoints ............................................................................................................ 4
   4.1. Primary endpoints ................................................................................................................ 4
   4.2. Secondary endpoints ............................................................................................................ 4
   4.3. Health economic endpoints ............................................................................................... 5
   4.4. Safety endpoints .................................................................................................................. 5
   4.5. Further Research Questions .............................................................................................. 5
   4.6. Lost to Follow-up / Drop - Outs ...................................................................................... 6
5. Statistical Analyses .................................................................................................................... 6
   5.1. Descriptive Analyses .......................................................................................................... 6
   5.2. Primary Analysis of the primary endpoints ....................................................................... 6
   5.3. Sensitivity Analyses of the primary endpoints .................................................................. 8
   5.4. Per protocol Analysis .......................................................................................................... 8
   5.5. Secondary endpoints ......................................................................................................... 8
   5.6. Health Economic Analyses ............................................................................................... 8
   5.7. Stratified Analyses .............................................................................................................. 9
   5.8. Further questions ............................................................................................................... 9
   5.9. Safety .................................................................................................................................. 10
   5.10. Interim Analyses .............................................................................................................. 10
6. Software ..................................................................................................................................... 10
7. Signatures .................................................................................................................................. 11
   7.1. Principal Investigator ......................................................................................................... 11
   7.2. Coordinating Investigator ................................................................................................. 11
   7.3. Deputy Coordinating Investigator .................................................................................. 11
   7.4. Statistician ......................................................................................................................... 11
   7.5. Health Economist .............................................................................................................. 11
   7.6. Data Management ............................................................................................................ 11
8. References ................................................................................................................................ 12
1. Objectives/Hypotheses

Primary objective
To assess the effect of acupuncture on rhinitis related quality of life and on rescue medication compared to minimal (sham) acupuncture in patients with seasonal allergic rhinitis.

Secondary objective
To assess the effect of acupuncture on rhinitis related quality of life and on rescue medication compared to rescue medication only in patients with seasonal allergic rhinitis.

2. Design

This study is a three-armed, randomised, controlled multicentre trial investigating the efficacy of acupuncture plus rescue medication vs. minimal (sham) acupuncture (a form of sham acupuncture involving superficial needling at non-acupuncture points) plus rescue medication, as well as the efficacy of acupuncture plus rescue medication vs. rescue medication alone in patients with seasonal allergic rhinitis (SAR), see Figure 1.
3. Populations for analyses

3.1. Intention to treat Population

The intention to treat population (ITT) includes all patients randomised with baseline data (i.e. for RQLQ less than 50% of the items in one or more of the seven question-complexes is missing in patient questionnaire 1 and RMS is not missing in patient diary 1).

3.2. Per protocol Population

The per protocol population (PP) includes all patients of the ITT population which were treated following the specifications of the study protocol without major protocol deviations.
Excluded from the per protocol population will be patients that meet at least one of the following criteria:

- No seasonal allergic rhinitis (SAR) to grass and birch pollen and/or no skin-prick and/or RAST test available or not test positive
- Visual analogue scale not > 40 mm and < 80 mm for SAR symptoms during the year before randomisation
- Use of oral or parenteral steroid, steroid or β²-adrenergic receptor agonist spray for more than one week continuously in the first 8 weeks after randomisation
- Auto-immune disorders and/or allergic asthma and/or moderate to severe atopic dermatitis
- Serious acute or chronic organic disease or mental disorder
- Specific immunotherapy < 3 years and/or any specific immunotherapy during the past two years or within the trial
- Any complementary and alternative treatment for SAR in the first 8 weeks after randomization
- No complete data for the primary end points RQLQ and RMS (week 6 to 8) available
- Not treated according to the allocated intervention group
- Start of intervention later than 2 weeks after randomisation (acupuncture and sham acupuncture group)
- Less than 10 interventions in the first 8 weeks (acupuncture and sham acupuncture group)
- Interruption of intervention of more than 3 consecutive weeks in the first 8 weeks (acupuncture and sham acupuncture group)
- Basic acupuncture points (L.I. 11, L.I. 4, L.I. 20, EX-HN 3 YINTANG = 7 needles) not used in at least 10 interventions in the first 8 weeks in the acupuncture group and at least 4 sham acupuncture points not used (= 8 needles) in the sham acupuncture group
- Acupuncture treatment during the first 8 weeks (rescue medication group)
4. Variables and endpoints

4.1. Primary endpoints

Primary endpoints are the patients averages of the Rhinitis Quality of Life Questionnaire (RQLQ)\(^1\) overall scores and the Rescue Medication Scores (RMS)\(^2\) of week 6 to 8 in the first year.

RQLQ regards the Rhinitis Quality of Life of the last days. To consider week 6 to 8 RQLQ is evaluated at week 7 and 8. Analyses are based on the mean of this two RQLQ scores.

The Rescue Medication Score (RMS) is a score of medication intake after one week, based on a daily evaluation. Analyses are based on the mean of these two RMS scores of week 7 and 8.

Oral medication of antihistaminic Cetirizine and the steroid Prednisolone were given as rescue medication to the patients. Detailed scoring for rescue medication and other anti-allergic or symptomatic medication taken by the patients is given in the following table.

<table>
<thead>
<tr>
<th>Medication</th>
<th>RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 mg Cetirizine (or equivalent 5 mg Loratadine, 5 mg Desloratadine, 5 mg Levocetirizine)</td>
<td>1</td>
</tr>
<tr>
<td>5 mg Cetirizine + 100 mg Pseudoephedrine</td>
<td>1</td>
</tr>
<tr>
<td>Topical steroids</td>
<td>1</td>
</tr>
<tr>
<td>Other topic antiallergic medication*</td>
<td>1</td>
</tr>
<tr>
<td>Other symptomatic medication**</td>
<td>1</td>
</tr>
<tr>
<td>20 mg Cetirizine</td>
<td>2</td>
</tr>
<tr>
<td>10 resp. 20 mg Cetirizine + topical steroid</td>
<td>2</td>
</tr>
<tr>
<td>Inhalation of steroids</td>
<td>2</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>3</td>
</tr>
<tr>
<td>Other topic antiallergic medication* + systemic steroids</td>
<td>3</td>
</tr>
</tbody>
</table>

* Cromoglycin acid, Azelastin, Levocabastin, Olopatadin
** Sinupret\(^a\), Gelomyrtol\(^b\), Gencydo\(^c\), Berberil Dry Eye AT\(^d\), Xylometazolin NS\(^e\)

4.2. Secondary endpoints

Secondary endpoints are:

- Disease specific quality of life as measured by the RQLQ score in week 16 in the first year and the average of RQLQ scores of week 6 to 8 in the second year
• The RMS in week 1 and the average of RMS in week 15 and 16 in the first year and the mean of RMS of week 6 to 8 the second year
• Responders to study intervention defined as patients with a change in RQLQ score of 0.5 or more between the baseline RQLQ score and the average of the RQLQ scores of week 6 to 8 in the first year
• VAS SAR overall symptom weekly between baseline and week 8, the average of week 15 and 16 in the first year and at baseline and in week 8 in the second year
• VAS SAR eye, nasal, pulmonary and pharyngeal symptoms at baseline, in week 8 and 16 in the first year and at week 1 and week 8 in the second year
• Global evaluation of study interventions, efficacy of interventions and global evaluation of study physicians in week 8 in the first year and in week 8 in the second year
• Global evaluation of total SAR symptoms in the first study year (recruitment year) and in the second study year (follow-up year) of each patient
• Health-related quality of life (SF-36) and in week 8 and 16 in the first year and in week 8 in the second year
• Cost analyses or cost-effectiveness analyses of acupuncture compared to standard treatment (rescue medication group) for the 2-year study period.

4.3. Health economic endpoints

Additionally, cost analyses of acupuncture and standard treatment compared to standard treatment alone (rescue medication group) will be conducted. Cost analysis will be supplemented by cost-effectiveness analysis, if the investigation shows a superior effectiveness in terms of overall quality of life (measured using SF-36) in acupuncture group.

4.4. Safety endpoints

Intervention related side effects and adverse events (AE), intermediate or serious adverse events (SAE) occurred during the study progress will be presented.

4.5. Further Research Questions

Further questions of this study are:
• Influence of patients expectancy on the average means of RQLQ overall score and the Rescue Medication Score (RMS) of week 6 to 8 in the first year
• Influence of physician expectancy on the average means of RQLQ overall score and the Rescue Medication Score (RMS) of week 6 to 8 in the first year
• The credibility of the respective treatment methods will be evaluated by analysing the questionnaire after the third acupuncture session in the acupuncture and sham acupuncture group.

• Influence of self reported measure of autonomic function and regulation (Havelhöher Konstitutionsfragebogen (T-HKF, Version 2.4) questionnaire) on the responders to study intervention to evaluate criteria of responders of acupuncture treatment.

• Patients estimation with reference to the intervention group they were randomly assigned

4.6. Lost to Follow-up / Drop-Outs

Number and the respective reasons (if available) of patients, which can not be followed up (lost to follow-up) or which withdrew from the study before the regular end (drop-outs) will be presented.

5. Statistical Analyses

5.1. Descriptive Analyses

All available data will be analysed descriptively for each intervention group. Results will be summarised as frequency of occurrence and percentages for nominal data. Results will be summarised as means, standard deviations, and 95%-confidence intervals for continuous data. Results will be summarised as medians, quartiles, and ranges for ordinal data. Differences in baseline variables will be analysed by appropriate tests (e.g. Chi-squared test, Kruskal-Wallis test, or analyses of variance) in pairwise comparisons between the three treatment groups.

5.2. Primary Analysis of the primary endpoints

As primary analyses, an analyses of covariance will be performed in the intention to treat population of the primary endpoints 1) the average of RQLQ scores of week 6 to 8 adjusting for the RQLQ score at baseline and 2) the average of Rescue Medication Scores (RMS) of week 6 to 8, adjusting for the RMS score at baseline. The test procedure will be hierarchical with one-sided tests and a type I error level of \( \alpha = 0.025 \):

(1) In a first step, acupuncture will be compared to penetrating sham acupuncture group using a test of non-inferiority with respect to RQLQ. The non-inferiority test is significant if the left-sided ANCOVA-based 97.5% confidence interval of the between-groups difference lies completely above the non-inferiority margin of -0.5.
Statistical Analyses Plan

Acupuncture for Seasonal Allergic Rhinitis (ACUSAR) – A Randomised Controlled Trial

(2) In case of significance in step 1, in a second step, acupuncture will be compared to penetrating sham acupuncture group using a test of non-inferiority with respect to RMS. The non-inferiority test is significant if the left-sided ANCOVA-based 97.5% confidence interval of the between-group difference lies completely above the non-inferiority margin of -1.5, chosen proportionally to the non-inferiority limit of RQLQ.

(3) In case of significance in step 2, in a third step, acupuncture will be compared to the sham acupuncture group with a test of superiority with respect to RQLQ or RMS. For this purpose, two left-sided ANCOVA-based 98.75% confidence interval of the between-group difference in RQLQ and RMS will be calculated and compared to zero. The test of superiority is significant if at least one of the two confidence intervals lies completely above zero.

Steps 4, 5, and 6 will be analogous to steps 1, 2, and 3, but with the rescue medication group instead of the sham acupuncture group.

Analyses will be adjusted for study centre (random effect), region (fixed effect) and year of randomisation (fixed effect) and will be performed within one model including the three intervention groups plus contrasts for each two-group comparison.

Partially missing RQLQ baseline items (i.e. less than 50% of the items in the one or more of the seven question-complexes) will be imputed using a mixed model\(^8\) based on the baseline mean value of the question complex (conditional) and on the values of the corresponding item at weeks 7 and 8 (marginal). The imputed dataset will be used for further computations. Missing RQLQ mean values at the 7th and 8th week and RMS values will be multiply imputed stratified by treatment group\(^8\) by including the following variables:\(^9\): baseline and follow up RQLQ and RMS scores, age, gender, recruiting centre, region, year, education, disease history and length of the treatment, other atopic diseases, severity of symptoms of hay fever, nasal, breathing, mouth- and throat problems in the week before the baseline evaluation was done, medical therapy in the last 8 weeks, foods avoided because of hay fever, CAM therapy in the last 12 months, symptoms of hay fever on a visual analogue scale in spring, and hyposensibilizing and allergen-specific immunotherapy, respectively.

Five thousand iterations will be done before the first imputation and 5000 iterations will be performed between successive imputations\(^1\). Multiple imputations will be performed using SAS PROC MI (SAS 9.1.3).
5.3. Sensitivity Analyses of the primary endpoints

The analysis of the primary endpoints will be repeated as described above with the last observation carried forward (LOCF) technique as a method for imputing missing endpoint values, and with an available case data set.

In case of relevant differences of baseline values additional adjustment(s) for these factors will be performed within the method described above.

5.4. Per protocol Analysis

The analysis of the primary endpoints will be repeated as described above for the per protocol population.

5.5. Secondary endpoints

The analyses of secondary endpoints will be performed by means of generalized linear mixed models (adjusted as described above) without the hierarchical testing procedure on the available case data set (without imputation of missing values).

5.6. Health Economic Analyses

5.6.1. Economic Perspective

All costs were analyzed from society’s perspective including direct and indirect costs. An additional analysis from third party payer’s perspective will be aimed.

5.6.2. Cost components

The following costs were considered:

- direct costs:
  - ambulatory services
  - inpatients treatments
  - adjuvant and remedies
  - medication
  - private expenditures
- indirect costs:
  - days of incapacity for work
  - reduced work schedule
5.6.3. **Hierarchical economic analysis procedure**

Cost analysis:
The cost analysis will be performed in a descriptive way including all relevant cost components collected during the study period. All cost components for the allergic rhinitis will be compared using the test procedure of secondary endpoints.

Cost-effectiveness:
Besides analyzing costs, effectiveness results have to be considered to get a comprehensive picture of economic aspects of acupuncture. For this purpose, the quality of life results measured by SF-36 were transformed into utilities (using a published algorithm). The subsequent calculation of QALYs (quality adjusted life years) is based on these utilities. In the case of superior QALY-results in acupuncture patients and additional costs, the incremental cost-effectiveness ratio (ICER) will be calculated to assess the cost-effectiveness-level. For calculation of cost-effectiveness acceptability curves, non-parametric bootstrap will be used.

5.6.4. **Sensitivity analysis**

In sensitivity analysis main parameters of health economic should be varied within realistic ranges. These parameters are:

- Mean costs per day of invalidity
- Mean costs per physician contact
- Costs per acupuncture treatment
- etc.

5.7. **Stratified Analyses**

For the primary endpoints analyses will be stratified to symptom score (VAS) before randomisation, age, gender, study centre, region and year of randomisation.

5.8. **Further questions**

Further variables will be included in the above described model to explore

- the influence of patients expectancy on the average means of RQLQ overall score and the Rescue Medication Score (RMS) of week 6 to 8 in the first year
- the influence of physician expectancy on the average means of RQLQ overall score and the Rescue Medication Score (RMS) of week 6 to 8 in the first year
- the influence of self reported measure of autonomic function and regulation (Havelhöher Konstitutionsfragebogen (T-HKF, Version 2.4) questionnaire) on the responders to study intervention.

The credibility of the respective treatment methods will be evaluated by analysing the questionnaire after the third acupuncture session in the acupuncture and sham acupuncture group.

The patients’ estimation with reference to the intervention group they were randomly assigned will be analysed descriptively.

5.9. Safety

Frequencies and percentages of safety endpoints will be presented overall and per treatment group. Chi-squared test or Fisher’s Exact test will be performed to compare treatment groups pairwise.

5.10. Interim Analyses

No interim analyses with respect to efficacy will be performed.

6. Software

Software used for analysing data:

- Microsoft Access 2003 (Microsoft Corporation, Redmond, USA)
- PASW Statistics 18 (SPSS Inc., Chicago, USA)
- SAS für Windows, Version 9.2 or higher (SAS Institute, Cary, NC, USA)
7. Signatures

7.1. Principal Investigator

Location, Date

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7.2. Coordinating Investigator

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7.6. Data Management

Sylvia Binting
8. References


