Efficacy and safety of Butterbur leaves extract Ze 339 in allergic rhinitis

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Landquart
Bousquet J, van Cauwenberge P, Khaltaev N. From Allergic Rhinitis and its Impact on Asthma (ARIA) in collaboration with the World Health Organization. 

# Therapy of allergic rhinitis

<table>
<thead>
<tr>
<th></th>
<th>Sneezing</th>
<th>Rhinorrhea</th>
<th>Nasal obstruction</th>
<th>Itching</th>
<th>Eye symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral H₁-Blockers</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>nasal</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>ocular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td><strong>Nasal steroids</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cromoglycates</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>nasal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>ocular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td><strong>Vasoconstrictors</strong></td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>nasal</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>oral</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Antileukotrienes</strong></td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>
Petasites hybridus
Butterbur extract Ze 339 in allergic rhinitis

1. Cultivation (Petzell®, leaves)
2. Extraction (non-critical CO₂)
3. Pharmacology, Pharmacokinetic
4. Clinical trials
   4.1. proof of principle
   4.2. Ze 339 vs. cetirizine
   4.3. Ze 339 vs. placebo, dose-finding
   4.4. Ze 339 vs. placebo and fexofenadine
5. Clinical evaluation
Cultivation (Petzell, leaves)
Stucture of Petasin

petasin chemovariety

furanopetasin chemovariety

petasin

isopetasin

neopetasin

S-petasin

S-isopetasin

S-neopetasin
### Extraction (non-critical CO₂)

1. **Total Σ of 6 petasins**  
   (petasin, neo- and isopetain; neo-S-petasin, S-petasin and iso-S-petasin)  
   **20.3 %**

2. **Total fatty acids**  
   - unsaturated cis-fatty acids: 1.1
   - poly unsaturated cis-fatty acids: 33.8
   - unsaturated trans-fatty acids: 0.0
   - saturated fatty-acids: 5.3  
   **40.2 %**

3. **Aroma components**  
   **7.0 %**

4. **Steroids/ Phytosterols**  
   **1.2 %**

5. **Pyrrolizidine alkaloids**  
   **n.d. (35 ppb)**

6. **Remainders**  
   (apolar const. without chromophors; water[ca. 6.0%])  
   **30 %**

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membrane phospholipids

arachidonic acid

cyclooxygenase-1 and -2

- prostaglandins and -cyclins
- thromboxane
(rheumatism, M. Alzheimer)

5 - lipoxygenase

- leukotrienes
(hay-fever, asthma, atopical dermatitis)

Ze 339
Role of petasin in the potential antiinflammatory activity of a plant extract of petasites hybridus.
OAR Thomet, UN Wiesmann, A Schapowal, Č Bizer, HU Simon
Biochemical Pharmacology (2001), 61: 1041-47
Inhibition of cysteinyll-leukotrienes in eosinophils and neutrophils
Inhibition of intracellular calcium by Ze 339 and petasin, but not by neopetasin and isopetasin
Pharmacology, Pharmacokinetic

Mode of action

* Leukotriene synthesis is inhibited

* Intracellular calcium ist blocked: release of inflammation mediators is blocked within 30 min (↓ ECP)
4. Clinical trials
4.1. Proof of principle (n=6)

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; day</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NASAL LAVAGE FLUID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTB&lt;sub&gt;4&lt;/sub&gt; (pg/ml)</td>
<td>313.1 ± 46.5</td>
<td>180.6 ± 32.2</td>
<td>180.6 ± 32.2</td>
</tr>
<tr>
<td>cysteinyl-LT (pg/ml)</td>
<td>137.0 ± 42.2</td>
<td>70.1 ± 16.5</td>
<td>70.1 ± 16.5</td>
</tr>
<tr>
<td>histamine (pg/ml)</td>
<td>153.7 ± 32.1</td>
<td>53.0 ± 8.4</td>
<td>53.0 ± 8.4</td>
</tr>
<tr>
<td><strong>SERUM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>petasin (ng/ml)</td>
<td>&lt; 2.0</td>
<td>7.7 ± 1.7</td>
<td>15.1 ± 2.3</td>
</tr>
<tr>
<td>ECP (µg/l)</td>
<td>18.7 ± 4.1</td>
<td>13.7 ± 3.5</td>
<td>11.5 ± 1.8</td>
</tr>
<tr>
<td><strong>URINE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>petasin (ng/mmol creatinine)</td>
<td>&lt; 2.0</td>
<td>&gt; 300.0</td>
<td></td>
</tr>
</tbody>
</table>

Very good effect on nasal obstruction: Normal rhinomanometry by day 6
4. Clinical trials
4.2. Ze 339 vs. cetirizine (Zyrtec®)

Inclusion criteria: allergic rhinitis (history), Prick-Test sneezing, rhinorrhea, itchy nose/eyes, nasal congestion 18 years and older
Exclusion criteria: alcohol- and drug abuse, pregnancy, child nursing consumptive diseases, transplantation
Assessment of quality of life: Allergy, 19: 5-34 (1994)
Primary variable: validated SF 36 questionnaire
4. Clinical trials
4.2. Ze 339 vs. cetirizine (Zyrtec®)

Randomised
n = 131

Butterbur Ze 339
n = 65

Efficacy Analysis
ITT: n = 61
PP: n = 51
protocol violation: n=10

Safety Analysis
ITT: n = 61
dropouts: n=4
1 asthma; 3 AE-GI

Cetirizine
n = 66

Efficacy Analysis
ITT: n = 64
PP: n = 51
protocol violation: n=13

Safety Analysis
ITT: n = 64
drop outs: n=2
withdr. info. consent, AE

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4. Clinical trials

4. 2. Ze 339 vs. cetirizine (Zyrtec®)

**Thesis:** Ze 339 is not inferior to cetirizine

**PRIMARY VARIABLES**

<table>
<thead>
<tr>
<th>Item</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td>physical function</td>
<td>0.001</td>
</tr>
<tr>
<td>emotional function</td>
<td>0.001</td>
</tr>
<tr>
<td>vitality</td>
<td>0.001</td>
</tr>
<tr>
<td>mental health</td>
<td>0.001</td>
</tr>
<tr>
<td>general health</td>
<td>0.001</td>
</tr>
<tr>
<td>physical activity</td>
<td>0.001</td>
</tr>
<tr>
<td>social functioning</td>
<td>0.001</td>
</tr>
<tr>
<td>pain</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Comparison of groups regarding the primary variables in SF-36 questionnaire (procentual differences begin vs. end of therapy)

1 physical function, 2 emotional function, 3 vitality, 4 mental health, 5 general health, 6 physical activity, 7 social functioning, 8 pain
4. Clinical trials

4.3. Ze 339 vs. placebo

Inclusion criteria: allergic rhinitis (history), Prick test sneezing, rhinorrhoea, itchy nose/eyes, nasal congestion
18 years and older

Exclusion criteria: alcohol and drug abuse, pregnancy, child nursing
consumptive diseases, transplantation

Severity of symptoms: FDA, Guidance for Industry, April 2000

Primary variable: sum of symptoms score
4. Clinical trials
4.3. Ze 339 vs. placebo

Randomised
n = 186

3 tabs. Ze 339
n = 60

Efficacy Analysis
ITT: n = 53
PP: n = 50
protocol violation: n=6

Safety Analysis
ITT: n = 53

2 tabs. Ze 339
n = 65

Efficacy Analysis
ITT: n = 57
PP: n = 54
protocol violation: n=7

Safety Analysis
ITT: n = 57

Placebo
n = 61

Efficacy Analysis
ITT: n = 55
PP: n = 50
protocol violation: n=8

Safety Analysis
ITT: n = 61
4. Clinical trials
4.3. Ze 339 vs. placebo

Self assessment - patient diary

Efficacy
4. Clinical trials
4.3. Ze 339 vs. placebo
4. Clinical trials
4.3. Ze 339 vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Patients</th>
<th>Percent</th>
<th>CHI-Square p</th>
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</thead>
<tbody>
<tr>
<td>Ze 339 3 tab.</td>
<td>51</td>
<td>56</td>
<td>91.0 %</td>
<td></td>
</tr>
<tr>
<td>Ze 339 2 tab.</td>
<td>44</td>
<td>62</td>
<td>70.9 %</td>
<td>&lt; 0.007</td>
</tr>
<tr>
<td>Placebo</td>
<td>27</td>
<td>59</td>
<td>45.7 %</td>
<td></td>
</tr>
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</table>
4. Clinical trials
4.3. Ze 339 vs. placebo

<table>
<thead>
<tr>
<th>PRIMARY VARIABLES</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 tablets are superior to placebo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2 tablets are superior to placebo</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 tablets are superior to 2 tablets</td>
<td>= 0.024</td>
</tr>
</tbody>
</table>
4. Clinical trials

4.4. Ze 339 vs. placebo and fexofenadine

Randomised
(ITT Population)
N=330

Fexofenadine
N=113
- Non-completers: 5
- Adverse Events: 2
- Consent withdrawal: 1
- Other reasons: 1

Butterbur Ze339
N=110
- Non-completers: 15
- Adverse events: 2
- Deterioration: 4
- Consent withdrawal: 8
- Other reasons: 1

Placebo
N=107
- Non-completers: 7
- Adverse events: 2
- Deterioration: 1
- Consent withdrawal: 4

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Efficacy of Ze 339 vs. fexofenadine and placebo

Hypothesis:
1. Ze 339 and fexofenadine are superior to placebo;
2. Ze 339 is not inferior to fexofenadine

Placebo (n = 107)
Ze 339 (n = 110)
Fexofenadine (n = 113)

Ze 339 vs. fexofenadine: one-sided equivalence (non-inferiority) p < 0.001
Efficacy of Ze 339 vs. fexofenadine and placebo

Improvement vs. baseline (%)
Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis.
A. Schapowal, BMJ 2002; 324: 1-4

Butterbur Ze 339 for the treatment of intermittent allergic rhinitis.
Dose-dependent efficacy in a prospective, randomized, double-blind, placebo-controlled study
A. Schapowal, Arch Otolaryngol Head Neck Surg. 2004; 130: 1381-1386

Treating intermittent allergic rhinitis: A prospective, randomized, placebo and antihistamine-controlled study of Butterbur extract Ze 339
A. Schapowal, Phytother Res 2005; 19: 530-537
Ze 339 / Tesalin® in clinical evaluation (n=103)

Symptoms at begin of therapy (mean on scale of 0-10 points)

Comparison of the means of symptoms: prior, during and after treatment
Ze 339 / Tesalin® in clinical evaluation (n=103)

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Conclusions

* Ze 339 inhibits leukotriene synthesis and intracellular calcium dose-dependently
* Onset of action 30 min after oral administration
* Ze 339 down-regulates all symptoms of allergic rhinitis
* Ze 339 is highly significant superior to placebo
* Ze 339 is not inferior to cetirizine and fexofenadine
* Ze 339 is safe (routine laboratory tests, urine analysis, ECG; toxicological data, mutation tests)
* Tesalin® is approved by Swissmedic since June 2003, has to be prescribed and has to be paid by health insurance since December 2003
* Investigations regarding atopic dermatitis and asthma are underway
Merci pour votre attention!

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