Released-active antibodies are innovative products for the effective management of severe respiratory viral infections

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Antibodies-based drugs are broadly studied and used

Application:
Autoimmune diseases; Cardiovascular diseases; Infectious diseases; Cancer; Inflammation

Limitations:
- Production
- Cost
- Pharmacokinetics
- Route of administration
- Safety

Approaches:
- Adjuvants
- Modification
- Encapsulation

Specific action + Neutralize the target

Technology of concentration reduction

Released-active form of antibodies

Specific action + Modify the target

Released-activity determined by initial substance derivatives’ emergence
TARGET MODIFICATION

Abs to IFNγ in RA form induces conformation changes of the IFNγ

Model: Nuclear Magnetic Resonance Spectroscopy

2-Dimension NMR-spectrum of IFNγ molecule
TARGET MODIFICATION

Abs to IFNγ in RA form enhance ligand-receptor interaction

Model: radioligand binding assay

Specific binding of \(^{125}\text{I}\)IFNγ with IFNγ receptor, % vs control

Picture was adapted from:
“The Interferons: Characterization and Application”
(Ed. By A. Meager) 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

* - p<0.05 vs Abs to TNFα in RA form, placebo
MODIFICATION OF BIOLOGICAL PATHWAYS

Abs to IFNγ in RA form increase the number of IFNγ producing cells

**Model:** production of IFNγ by PBMC *in vitro*

![Diagram of IFNγ production and receptor activation]

**IFNγ producing cells, per 4*10^5 PBMC**

- Control
- RAF of Abs to IFNγ
- Medium

* - p<0.05 vs control

Picture was adapted from:
"The Interferons: Characterization and Application" (Ed. By A. Meager) 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
Anaferon
Abs to IFNγ in RA form

Launched in 2001-2002
Registered in 17 countries

The most prescribed pediatric medicine in Russia (2012)
Brand №1 in Russia 2013 prize in antiviral medicines

Publications in peer-reviewed Russian and international journals
Target: IFN\(\gamma\)  
Agent: Abs to IFN\(\gamma\) in RA form

**Anaferon is effective in treatment of MERS-CoV infection**

Viral load of MERS-CoV in infected cells, Log 10 CDU/ml

- Anaferon
- Control
- Virus
- PEG-IFN \(\alpha\)-2b
- No virus

\(*, \# - p<0.05\) vs PEG-IFN \(\alpha\)-2b-treated group, virus control
Anaferon is effective against pandemic influenza strain H1N1

Target: IFNγ

Agent: Abs to IFNγ in RA form

Viral load in lungs of mice inoculated with ID₁₀₀ Influenza virus A/California/07/2009 (H1N1)Victoria, log TCID₅₀/ml

* - p<0.05 vs control
Anaferon is effective against ‘swine flu’ (A/H1N1)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Virus dose</th>
<th>Survival/total (% survival)</th>
<th>Mean day to death ± SEM</th>
<th>Index of protection (%)</th>
<th>Lung data</th>
<th>Medium size of foci of pneumonia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC*</td>
<td>1 LD50</td>
<td>7/20 35%</td>
<td>20.1 ± 0.9*</td>
<td>89.5</td>
<td>5.1 ± 0.9*</td>
<td>17.2 ± 4.7*</td>
</tr>
<tr>
<td></td>
<td>10 LD50</td>
<td>2/20 10%</td>
<td>11.3 ± 1.7</td>
<td>25.7</td>
<td>nd^4</td>
<td>nd^4</td>
</tr>
<tr>
<td>Oseltamivir (20 mg/kg/day)</td>
<td>1 LD50</td>
<td>10/20 50%</td>
<td>19.7 ± 0.9*</td>
<td>78.9</td>
<td>3.4 ± 0.6*</td>
<td>9.2 ± 3.0*</td>
</tr>
<tr>
<td></td>
<td>10 LD50</td>
<td>7/20 35%</td>
<td>7.9 ± 1.0</td>
<td>-2.9</td>
<td>nd^4</td>
<td>nd^4</td>
</tr>
<tr>
<td>AC* + Oseltamivir (20 mg/kg/day)</td>
<td>1 LD50</td>
<td>20.9 ± 0.1*</td>
<td>89.5</td>
<td>nd^4</td>
<td>3.1 ± 1.2*</td>
<td>16.5 ± 4.5*</td>
</tr>
<tr>
<td></td>
<td>10 LD50</td>
<td>13.3 ± 1.8*</td>
<td>nd^4</td>
<td>-29.0</td>
<td>6.3 ± 0.4*</td>
<td>34.5 ± 4.6*</td>
</tr>
<tr>
<td>Control (no treatment)</td>
<td>1 LD50</td>
<td>21/40 (52.5%)</td>
<td>15.8 ± 0.9</td>
<td>0</td>
<td>nd^4</td>
<td>nd^4</td>
</tr>
<tr>
<td></td>
<td>10 LD50</td>
<td>15/40 (37.5%)</td>
<td>7.9 ± 0.9</td>
<td>0</td>
<td>nd^4</td>
<td>nd^4</td>
</tr>
<tr>
<td>Uninfected (no treatment)</td>
<td>0</td>
<td>10/10 (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fig. 1. Dynamics of body weight of mice in the course of pneumonia caused by influenza virus A/California/7/09 (H1N1).v.

**Table 1**

Protective activity of AC* against influenza A(H1N1) 2009-caused lethal pneumonia in BALB/c mice. When P < 0.05 values are indicated in bold.

Anaferon increases the efficacy of Oseltamivir in treatment of Oseltamivir-sensitive strain of Influenza virus (A/H1N1pdm09).

Viral load of H1N1/A (Danemark/524/09 sen) in infected cells, Log10 copies/mL

* * - p<0.05 vs Oseltamivir-treated group, virus control
INFLUENZA

**Target:** IFNγ  
**Agent:** Abs to IFNγ in RA form

Anaferon is effective in treatment of Oseltamivir-resistant strain of Influenza virus (A/H1N1pdm09)

Viral load of H1N1/A (Danemark/528/09 res) in infected cells, Log10 copies/mL

Days after infection

*, # - p<0.05 vs Oseltamivir-treated group, virus control
Ergoferon proven clinical efficacy by randomized double blind placebo control trials

ClinicalTrials.gov Identifier: NCT01843842

Eligibility: both sexes, age 3-18, consultation and therapy within 24 h after the onset infection.

Randomized (n=162)

Allocated to Ergoferon (n=82)
Allocated to Placebo (n=80)

Analysis

Primary criteria: % patients demonstrating recovery/improvement in health
Secondary criteria: Dynamics of fever; Proportion of patients with normal body temperature; Severity of clinical manifestations; Severity of acute respiratory infection course; Number of intakes of antipyretics; Proportion of patients with exacerbation of the disease course

Percentage of patients with recovery/improvement in health

Morning

Day 2 | Day 3 | Day 4
6 | 14 | 20

Evening

Day 2 | Day 3 | Day 4
14 | 14 | 61

Ergoferon | Placebo

* - p<0.05 vs placebo

Ergoferon proven clinical efficacy comparable to Oseltamivir by multicenter open-label randomized trials

ClinicalTrials.gov
ClinicalTrials.gov Identifier: NCT01804946

Study design:
- Both sexes
- Age 18-60
- 12 research centers

Ergoferon proven clinical efficacy comparable to Oseltamivir by multicenter open-label randomized trials

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration of symptoms, days</th>
<th>ITT analysis</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=78)</td>
<td>Group 2 (n=78)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>2.1 ± 1.5</td>
<td>2.3 ± 1.6</td>
<td>Δ = -0.13; 95% CI &lt; 0.28</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>t = -2.4; p = 0.01</td>
</tr>
<tr>
<td>Flu-related non-specific symptoms</td>
<td>2.7 ± 2.2</td>
<td>2.4 ± 2.1</td>
<td>Δ = 0.29; 95% CI &lt; 0.47</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>t = -1.7; p = 0.04</td>
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<tr>
<td>Respiratory symptoms</td>
<td>2.8 ± 2.5</td>
<td>2.6 ± 2.6</td>
<td>Δ = 0.15; 95% CI &lt; 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t = -2.1; p = 0.02</td>
</tr>
<tr>
<td>All influenza symptoms</td>
<td>2.7 ± 2.3</td>
<td>2.5 ± 2.2</td>
<td>Δ = 0.22; 95% CI &lt; 0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t = -3.0; p = 0.001</td>
</tr>
</tbody>
</table>

**Preclinical studies**

- Single-dose toxicity
- General toxicity
- Potential mutagenic properties
- Allergenic properties
- Reproductive toxicity
- Effect on postnatal development
- Immunotoxicity

**Results**

- No toxic effects have been revealed
- No mutagenic properties have been revealed
- No toxic effects on lactating females (general condition, BW gain) and postnatal development

**Clinical safety**

- No severe adverse events reported
- Can be safely used in combination with symptomatic and other drugs, on a long term basis / in patients with immunodeficiencies
- Do not cause exhaustion of the immune system

**STRONG SAFETY**
TAKE-HOME MESSAGES

- Modifying activity of the RA drugs
- High safety and absence of adverse effects
- High efficacy in severe respiratory infections management
- Standard drugs’ efficacy increase in conjoint use

Released-active drugs represent promising opportunity for being included in standard treatment schemes
Thank you for your attention

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