

# Palivizumab and respiratory syncytial virus disease: Selling sickness for future?

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**Abstract.** Over the past two decades Russia has gone through dramatic “democratic” changes resulting in unprecedented deterioration of health, loss of lives and extinction of population. The health system turned into a ridiculous monster of poorly organized business exploiting reminiscent social values of the past to build profits on selling sickness-for-all in consumer culture.

We present facts and conclude that introduction of palivizumab into clinical practice for the most vulnerable patient category was done without confirmation of efficacy, without pharmacoeconomics evaluations, without any precautionary measures in a country with undeveloped pharmacovigilance system.

The situation calls for immediate action of responsible authorities and the society as a whole.

Therapeutic use of monoclonal antibodies is one in a series of “innovative” technologies of modern clinical medicine and health systems. Search for new targets for pharmaceuticals is stimulated by far not by practical therapeutic need but much more by financial incentives since the technologies are attractively costly. Recent introduction of monoclonal antibodies for respiratory syncytial viral infection (RSV) prophylaxis into routine pediatrics practice raises serious concerns since the target is the most vulnerable patient group – infants and neonates.

Palivizumab (a humanized monoclonal antibody produced by recombinant DNA technology) was registered in Russian Federation in 2010. Information on palivizumab, called instruction for use in medicinal practice, appeared on the official state website of registered medicines (<http://grls.rosminzdrav.ru/>) only in November 2013 as a manufacturer’s instruction for administration, registered with the Ministry of Health on the 5th of March 2013 [1]. This information does not contain a section on approved indications for use at all. In 2013 changes in the instruction for use were made, these changes solely constitute the information on the Ministry of Health website, not the instruction for use itself. Thus, the use is guided by manufacturer’s recommendations, which have not been substantiated by sound clinical evidence.

Approval of palivizumab (Synagis) by FDA and EMA was based on the results of two randomized double-blind placebo controlled trials, which used only secondary end-point of hospitalization due to RSV infection as an efficacy outcome. The first trial called Impact-RSV (1998) included 1502 children under 24 months of age with bronchopulmonary dysplasia (BPD) and premature infants born before and

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on the 35th week of gestation, who were under 6 months of age at the trial entry. The trial was conducted during a single RSV season. The outcome – hospitalization rate in palivizumab group was 4,8% (48/1002), and it was 10,6% (53/500) in placebo group [2]. The second trial [3] included 1287 children less than 24 months of age with hemodynamically significant congenital heart disease and it was conducted over four consecutive RRSV seasons. Hospitalization rate in palivizumab group was 5,3% (34/639), in placebo group – 9,7% (63/648) [3]. Analysis of these results showed that the number of patients who would need to be treated for prophylaxis with 5 injections in order to prevent 1 hospitalization due to RSV infection (NNT value) was 17 in the first trial and 23 in the second one. It is very doubtful that these high NNT values and the use of secondary end-points (hospitalization) as an outcome measure could justify prophylactic use of the drug in the entire population at risk of severe RSV-infection.

Authors from Canada conducted additional subgroup analysis in these two studies [2, 3] and found that *«for children older than 6 months of age the NNT was 83»* [4]. How could it happen that with the NNT values for the non-clinical outcome (hospitalization) at around hundred coupled with potential risks of adverse reactions and not precisely determined risk of RSV infection at all the use of Synagis became a routine practice?

This is an ugly example of preventive use of palivizumab in the entire population at “sold” risk of not precisely determined disease.

The data of post-marketing studies of effectiveness, safety and cost-effectiveness of palivizumab are quite contradictory and do not allow for reliable conclusions on sound clinical recommendation on its use.

The authors of recently published Cochrane systematic review *«Monoclonal antibody for reducing the risk of respiratory syncytial virus infections in children»* [5] present the conclusions of effectiveness of palivizumab prophylaxis in reducing hospitalization rate due to RSV-infection and uncertainty about cost-effectiveness of this intervention. However, the authors point out that all 7 included clinical trials were sponsored by the manufacturer of palivizumab. Interpretation of the results of palivizumab's pharmacoeconomics based on 34 studies reporting on cost-effectiveness of palivizumab prophylaxis, is also difficult: *«ICER [incremental cost-effectiveness ratio] values varied considerably across studies, from highly cost-effective to not cost-effective»*. No wonder, that many of the studies supporting cost-effectiveness of palivizumab prophylaxis of severe RSV-infection in high-risk children, were sponsored by pharmaceutical company [6–14], or had authors with direct conflict of interests [15–24], which suggests the possibility of the risk of bias in the reported study findings. And on the contrary, the studies, which were not sponsored by pharmaceutical industry, or the studies authored by researchers who declared that they had no conflict of interest, concluded on more limited prophylactic use of palivizumab [25–28] or did not support cost-effectiveness of such an intervention at all [29–32]. Post-marketing independent controlled clinical trials of sufficient quality have never been performed.

So what do the regulators (the European Medicines Agency (EMA) and Food and Drug Administration (FDA) of the USA) do and what information do they release after granting marketing authorization for palivizumab? In 2004 EMA on the basis of 5 year studies concluded that *«based on the CHMP (Committee for Medicinal Products for Human Use) review of the available information, the CHMP considered that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of Synagis continues to be favourable»* [33]. The FDA and MedImmune recently revised the Warnings and Post-Marketing Experience sections of the Synagis (palivizumab) label and proposed the following changes: to add in the Warnings section “Cases of anaphylaxis and anaphylactic shock, including fatal cases” have been reported following initial exposure or re-exposure to Synagis”; to move the information on symptoms of acute

hypersensitivity from the Post-Marketing Experience section, and to add the symptom of hypotension to the Warnings section; to add “a drop in blood pressure” to the “Who should not receive Synagis?” and to add “Such reactions may be life-threatening or cause death” to the “Possible, serious side effects include” section of Patient Package Insert [34].

Lack of adequate and mandatory safety evaluation of the preparation of monoclonal antibodies in long-term patient monitoring causes great concern. Information on adverse reactions to palivizumab in post-marketing period is scarce because it comes only from voluntary reporting. Available limited data reveals poor safety profile, well-known adverse effects of monoclonal antibodies have been already reported for palivizumab also: blood and lymphatic system disorders (leucopenia, severe thrombocytopenia), immune system disorders (anaphylaxis and anaphylactic shock; in some cases, fatalities have been reported), vascular disorders (haemorrhage), general disorders and administration site conditions (fever, injection site reaction), skin and subcutaneous tissue disorders (rash, eczema) and others (convulsions, apnea, abnormal liver function tests) [35]. It would be hopeless to wait from a pharmaceutical manufacturer of expensive medicine truthful information on adverse effects profile. An economic evaluation without complete data on adverse effects data also does not make any sense. In its package insert the manufacturer points out that the studies showed the safety profile of palivizumab and placebo to be the same. This information is wrong and misleading; it creates false impression of safety and lack of any risks.

Simple calculations show that such a doubtful “prophylaxis” is unaffordable for the society:

The price of one 50 mg vial in Russian Federation is around 53 thousand rubles. The course of 5 injections for a single patient costs approximately 265 thousand rubles (equals to 6 624 Euros or 8 833 US dollars). If we compare these costs and a regular physician’s salary in the Russian Federation, we see that the cost of one 5-injection course for a single patient equals to 38 monthly salaries. In other words a physician would have to work for 3 years and 2 months to earn just enough money to cover the costs of palivizumab treatment for one patient. However health facilities purchase Synagis for millions of rubles. For example a state city hospital for children with 230 beds in 2012 purchased 87 vials for nearly 5 million rubles accounting for 13% of the hospital’s drug budget.

We conclude that introduction of palivizumab into clinical practice for the most vulnerable patient category was done without confirmation of efficacy, without adequate pharmacoeconomics evaluations, without any precautionary measures; and in case of Russia – in a country with undeveloped pharmacovigilance system. Furthermore, since the end of 2012, palivizumab was included in the “National Clinical guidelines for chronic respiratory diseases in children, developed in perinatal period”, approved by the Ministry of health of Russian Federation.

The situation calls for immediate action of responsible authorities and the society as a whole.

### **Conflict of interest statement**

We declare that we do not have any conflict of interest.

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