Biotechnology Advances xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Clinical, technological, and economic issues associated with developing new lung surfactant therapeutics

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ABSTRACT

Discovery of lung surfactant deficiency as a main cause of neonatal respiratory distress syndrome (NRDS) has influenced a steep increase in lung surfactant research. Although this has yielded impactful scientific discoveries, much of the basic research on lung surfactants has failed to translate into clinical practices. This is attributed to insufficient information covering the entire lung surfactant ecosystem, from the basic science to economics surrounding the development and clinical practices. In this manuscript, developments related to improving therapeutic lung surfactant as well as the degree of unmet need are analyzed from both technical and economic perspectives. Two potential opportunities are emphasized: (1) aerosolized lung surfactants to treat NRDS infants, and (2) synthetic lung surfactants for acute respiratory distress syndrome (ARDS) patients. Each has a modestly projected US market size of $120 million and $4 billion, well enough to make up for the high development costs associated with investigational drug development. Both opportunities have been pursued in the past, but to date these attempts have met with no success mainly due to technical limitations. With the recent advancements in both fields, technology improvements have created opportunities to solve both decades-old problems.

1. Introduction

Lung surfactant is a great example of how knowledge in basic science can translate into a life-saving product. Without lung surfactants our lungs would disproportionately collapse due to imbalance in lung alveoli pressures. The remarkable physicochemical behaviors of lung surfactants have been well studied for the past few decades. However, today there still lies a gap in the available literature necessary to link the clinical practices, basic science, and the pharmacoeconomics of therapeutic lung surfactants. This article contains an analysis of the entire therapeutic lung surfactant ecosystem and identifies the requirements for the next generation of therapeutic lung surfactants. We would like to note that readers interested in basic biology, biochemistry and physiology of lung surfactants should consult other sources such as the references listed in References (Notter, 2000; Lachmann, 1989; Nag, 2005; Robertson and Taeusch, 1995; Khubchandani and Snyder, 2001; Kingma and Whitsett, 2006; Sato et al., 2010).

2. The US lung surfactant market is currently saturated with three well-established products

In current clinical practices, therapeutic lung surfactant indications are limited to neonatal respiratory distress syndrome (NRDS) and meconium aspiration syndrome (MAS). The two indications are both infant-related, but differ in terms of gestation period and mechanism. NRDS is caused by lung surfactant deficiency in premature infants, whereas MAS is caused by lung surfactant deactivation in post-term infants when they aspirate meconium stained amniotic fluids. The prevalence for NRDS is 10 out of 1000 infants, and the prevalence for MAS is 0.43 out of 1000 infants (Dargaville and Copnell, 2006). The higher prevalence of NRDS over MAS has led to NRDS being the indication of focus during the development history of therapeutic lung surfactants. In this section, NRDS is discussed first, while MAS is revisited in a later section along with acute respiratory distress syndrome (ARDS).

When infants are born preterm, without the full production of lung surfactants, the lungs are collapsed and are unable to provide sufficient levels of oxygen. To address this issue, the first approach was to increase the level of oxygen delivered to the infant's lungs using ventilators. In the late 1960s mechanical ventilators improved substantially, and the infant survival rates increased from 23% to 70% (Cumarasamy et al., 1973). Another treatment that helped to improve the infant survival rates from NRDS was antenatal corticosteroid treatments. Infants' mothers treated with corticosteroid 24 h before giving birth were shown to reduce the infant's chance of developing NRDS by 50% (Liggins and Howie, 1972; Crowley, 1995).

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https://doi.org/10.1016/j.biotechadv.2018.03.017
Received 19 December 2017; Received in revised form 20 March 2018; Accepted 23 March 2018

Table 1
Comparison of the three animal extracted lung surfactant therapies marketed in the US. More detailed information regarding these products can be found in References (Notter, 2000; Zhang et al., 2011; Curosurf.com, 2018).

	Curosurf (Chiesi)	Infasurf (ONY)	Survanta (AbbVie)
Source	Porcine lung mince	Calf lung lavage	Bovine lung mince
Phospholipid concentration (mg/ml)	76	35	25
SP-B (mg/ml)	0.45	0.26	0.01
SP-C (μg/μM phospholipid)	5.0–11.6	8.1	1.0–20.0
Cholesterol (mg/ml)	0	2.0–3.0	< 0.06
Dose volume (ml/kg)[a]	2.5	3	4
Surfactant dose (mg/kg)	200	105	100

[a] The dose volume is for the first initial recommended dose. Recommended additional doses are: up to 2 additional doses (total 3 doses) of 1.25 ml/kg per dose for Curosurf with 12 h intervals, up to 2 additional doses of 3 ml/kg per dose for Infasurf with 12 h intervals, and up to 3 additional doses of 4 ml/kg per dose for Survanta with at least 6 h intervals in the first 48 h after birth.

In the 1950s, Avery and Mead discovered the root cause of NRDS to be from lung surfactant deficiency; (Avery and Mead, 1959) this finding was the start of a new wave of research on lung surfactants, both basic and clinical. By the 1990s, therapeutic lung surfactants extracted from animals became available in clinical practices. This so-called surfactant replacement therapy using animal extracted lung surfactants has led to decreasing the NRDS-related mortality rates down to < 2%. Over the years different animal extracted lung surfactants entered the market with variations in their formulation preparation. In the US, there are currently three animal extracted lung surfactants; Survanta (AbbVie), Curosurf (Chiesi), and Infasurf (ONY), with Survanta being the first to enter the US market followed by Infasurf and then Curosurf. A detailed comparison of the three products is shown in Table 1.

In addition to the different compositions of the therapeutic lung surfactants, the business strategies used for the three products are also different. Chiesi and ONY are small sized pharmaceutical companies, and sales of therapeutic lung surfactants are their primary focus, whereas AbbVie, being a large sized pharmaceutical company, utilizes Survanta as a doorway to access the hospital formularies to promote their infant nutrition products (NSF I-Corps Interviews, 2017). This strategy has kept the price of Survanta low, $600–800 per treatment, despite it being a life-saving product (NSF I-Corps Interviews, 2017). Comparatively, other life-saving products such as cancer drugs are priced around $30,000 per treatment (Siddiqui and Rajkumar, 2012). For small pharmaceutical companies such as Chiesi and ONY, the low price standard set by AbbVie limits their pricing tactics. When Infasurf and Curosurf first entered the US market they were offered at discount prices of 15% and 30% off, respectively (NSF I-Corps Interviews, 2017). Chiesi's response strategy to AbbVie was to use aggressive marketing to capture the majority market share (NSF I-Corps Interviews, 2017).

To acquire the majority of the market share, Chiesi promotes that Curosurf achieves higher performance when compared to Survanta and Infasurf. Dissecting this claim, Curosurf has a lower dose volume of 2.5 ml/kg, which is claimed to be advantageous in reducing the risk of blockage during the intratracheal instillation procedures (Wiseman and Bryson, 1994). However, a lower liquid dose can limit even distribution of the lung surfactants and reduce the overall amount of active ingredient delivered to the deep lungs (Halpern et al., 1998; Filoche et al., 2015). Chiesi has supported many research studies and clinical trials directly comparing Curosurf to other products to acquire evidence of the product's superiority (Speer et al., 1995; Ramanathan et al., 2013; Cogo et al., 2009). From a clinical and scientific perspective, controversies still remain on which formulation truly is most effective, but from the sales data, Chiesi was successful in capturing a majority of the market share as shown in Fig. 1. Interestingly, most of the market share gains made by Curosurf have come from Survanta's market share. This is speculated to be due to the combination of AbbVie's low focus on marketing Survanta and the product's extremely low SP-B level.

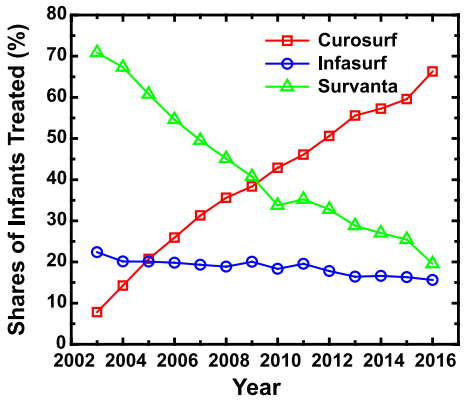

Fig. 1. Shares of infants treated with Curosurf, Infasurf, and Survanta in the US from 2003 to 2016. Data were extracted from IMS lung surfactant market purchases from May 2004 to December 2012 and Symphony SHA lung surfactant purchases from January 2013 to September 2016.

3. For investigational new drug development, the market size needs to be in the hundreds-of-million-dollar range to recover the high development cost

As in any other field, development priority is given to products that have a significant clinical impact and can overcome the costs associated with development. Typically, the development phase is expected to take around 10 years to complete with the majority of costs being associated with required clinical trials that average $33.4 million (Martin et al., 2017). From a clinical perspective, there is still room for improvement in the current lung surfactant formulation. One example is that the clinical outcomes in terms of NRDS-related mortality for low birth weight infants are significantly different depending on the product used. A retrospective observational cohort analysis performed by Ramanathan et al. shows a mortality rate of 11.72% for 500–749 g birth weight infants treated with Curosurf compared to 17.39% for Infasurf and 20.67% for Survanta (Ramanathan et al., 2013). Another example that shows the need for further formulation optimization is the result of a lower infant mortality rate when treated with a higher dose of Curosurf (200 mg/kg) compared to a lower dose of Curosurf (100 mg/kg) (Ramanathan et al., 2004). In a side-by-side comparison clinical trial of Curosurf versus Survanta (N = 293), the 200 mg/kg (= 80 mg/ml × 2.5 ml/kg) dose of Curosurf exhibited a significantly lower mortality rate of 3.0% compared to 6.25% for 100 mg/kg (= 80 mg/ml × 1.25 ml/kg) Curosurf and 8.16% for 100 mg/kg (= 25 mg/ml × 4 ml/kg) Survanta (Ramanathan et al., 2004). In a different clinical trial, the efficacies of 120 mg/kg (= 30 mg/ml × 4 ml/kg) and 60 mg/kg (= 30 mg/ml × 2 ml/kg) doses of Surfactant-TA (Tokyo Tanabe) were compared (N = 46) (Konishi et al., 1988). Although mortality rates were comparable between the two dose levels, the incidences of intraventicular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) were significantly less in the higher dose group. These clinical trial results suggest that improving the current lung surfactant formulation could result in saving more premature infants from NRDS-related conditions as well as complications that typically arise down the road. Unfortunately, the question, which lung surfactant composition at what dose level yields the best clinical efficacy remains unanswered; a conclusion could only be drawn when results from a large-scale randomized clinical trial involving all products become available. Thus far, clinical investigations comparing different products mainly involved either side-by-side comparisons of two products (e.g., Curosurf vs.