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Botulinum toxin drugs: brief history and outlook

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Abstract The global botulinum toxin (BT) market is currently undergoing rapid changes: this may be the time to review the history and the future of BT drug development. Since the early 1990s Botox® and Dysport® dominated the international BT market. Later, Myobloc®/NeuroBloc®, a liquid BT type B drug, came out, but failed. Xeomin® is the latest major BT drug. It features removal of complexing proteins and improved neurotoxin purity. Several new BT drugs are coming out of Korea, China and Russia. Scientific challenges for BT drug development include modification of BT's duration of action, its transdermal transport and the design of BT hybrid drugs for specific target tissues. The increased competition will change the global BT market fundamentally and a re-organisation according to large indication groups, such as therapeutic and cosmetic applications, might occur.

Keywords Botulinum toxin · Therapeutic use · History · Future perspectives · Global market

Introduction

The international botulinum toxin (BT) market is currently undergoing rapid changes: Allergan, the world's largest BT manufacturer, was taken over by Actavis, a generics manufacturer, with no previous connections to the BT market. Asian competition is rising with Korea alone now preparing three new BT products for international competition. This may be a good time for a closer look to where BT drugs have come from and to where they might be heading for.

Botox® and Dysport®

Thanks to the ingenious idea of Alan B Scott and to the ground-breaking manufacturing by Edward Schantz and Eric A Johnson, BT type A has been used therapeutically since the early 1980s with tremendous success to treat muscle hyperactivity disorders (Scott 1980). Cosmetic effects also based on muscle relaxation were discovered and commercialised later (Carruthers and Carruthers 1992). Most recently, intrinsic analgesic effects of BT have been described in chronic migraine (Aurora et al. 2011). Today, BT is used in at least nine different medical specialties for more than 30 major indications (Dressler 2013).

Scott originally registered the Schantz and Johnson product under the name Oculinum® through his Oculinum Company. In 1991 the company together with 125 mg of the original BT batch 79/11 was sold to Allergan of Irvine, CA who renamed the drug Botox® and used the original batch as the exclusive source for their drug until 1998 when a continuous manufacturing process was introduced. Later, with the emerging cosmetic use special brand names (Vistabel®, Botox® Cosmetic) were introduced. In response to that, the United States Food and Drug Administration suggested in 2009 non-proprietary names for BT drugs suggesting onabotulinumtoxinA for all of Allergan's BT drugs.

Parallel to the United States development, a BT product was developed in the United Kingdom by the Public Health Laboratory Service in Porton Down, Wiltshire. In 1992 it

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was licensed in Europe under the brand name Dysport® and later the non-proprietary name abobotulinumtoxinA. After several changes in ownership the company was finally acquired by Ipsen of France who subsequently sold the cosmetic operations to Galderma of Switzerland distributing the product as Azzalure®. Allergan and Ipsen developed the US and European markets by seeking registrations for numerous indications thus acquiring intellectual property for a substance which is as such not patentable.

New competition

Started in the US and Europe with just a few neurological indications, BT therapy reached many medical specialties and all continents (Dressler 2013). This growth in therapeutic diversity and geographic distribution revealed BT's real potential. In the meantime, a global market with estimated annual sales in excess of 5–6 billion US dollars has emerged, half of it in therapeutic uses and half in cosmetic uses.

In 2000, Elan introduced Myobloc®/Neurobloc® (rimabotulinumtoxinB), a BT drug based on BT type B and stabilised as a ready-to-use solution. However, antigenicity problems and adverse effects prevented a wide-spread use. Elan's financial problems in the stock market turmoil of the Enron crisis didn't help the product either.

Quietly, the public food safety laboratory in Lanzhou, Gansu Province, China developed its own BT type A product which started to be used in China in the late 1990s. Re-packaged under an amazing variety of phantasy names and often mimicking the Botox® brand name, it is now widely distributed in Asia and South America. A second genuine source of BT may now exist in China.

In 2005, a new BT type A drug was launched in Germany by Merz Pharmaceuticals as Xeomin® (incobotulinumtoxinA). It contains purified botulinum neurotoxin and complexing proteins are removed. An advanced manufacturing process yields botulinum neurotoxin with superior specific biological potency and, thus, reduced antigenicity. Whether removal of the complexing proteins contributes to the product's improved antigenicity remains unclear.

Global competition

The biotechnology revolution, one of the megatrends at the beginning of the third millennium, further stimulated the BT market as BT can be perceived as a classical biotech product with its special manufacturing technology and its typical business model. In Korea, there are currently three BT manufacturers: Medytox with Neuronox®, a conventional BT type A drug, Hugel with Botulax®, another conventional BT type A drug, and Daewoong with Nabota®/DWP-450, a conventional BT type A drug with a special purification process. Interestingly, Daewoong's registration program this time also includes the United States. Medytox is now developing a second BT drug named MT101017 without complexing proteins and free of human serum albumin. China's Lanzhou drug continues its expansion into more developed markets such as Russia, where it already has the widest spectrum of licensed indications of all registered BT drugs. Russia itself has come up with Relatox®, a conventional BT type A drug manufactured by Mikrogen. PurTox®, a development project for another BT drug free of complexing proteins, was originally started by Mentor of Santa Barbara, California and later acquired by Johnson & Johnson, but was aborted in the meantime.

Future developments

Market development so far was dominated more by economy than by science. Where are the real innovative ideas? Where are the scientific challenges?

Innovation could focus on BT's mode of action. Several companies are thinking about BT drugs with a shorter or a longer duration of action. Whereas markets for short-acting BT drugs may be few, long-lasting BT drugs can be an advantage for many patients with stable injection schemes.

Innovation could also focus on the BT application. All drugs have to be transported across the skin to reach their target tissues. Conventionally, this is achieved by an injection needle placed in the target tissue. In sensitive skin areas as the palm or the sole of the foot this may be unpleasant. Ways to reduce this injection site pain have been developed including pH modification of the reconstituted BT drug (Dressler et al. in press) or using inhalative anaesthesias (Paracka et al. 2015). BT drugs with the ability to penetrate the skin barrier would be an advantage especially for aesthetic and dermatological applications. Revance Therapeutics of Newark, CA has suggested to use their TransMTS® proteins as carriers to transport BT transcutaneously. Principle questions, however, remain open.

Other speculations include the use of carriers to keep the injected BT within the target tissues thus reducing BT washout and increase effective BT doses. Transdermal Corporation of Birmingham, MI is trying to use their Trans Ionic Nanoparticle Technology (InParT™) for this purpose.

Some of the most visionary projects are currently discussed at Syntaxin, now subsidiary of Ipsen. Their general approach under the name of targeted secretion inhibition is

to use hybrid BT compounds to block secretion in various cell populations including secretion of growth hormone or cancer messenger substances. More practically, Syntaxin has modified BT to better target cells involved in pain processing.

The global BT market is currently characterised by increased competition and abundant liquidity. Traditionally, this drives re-organisation. With the rapidly growing number of BT indications, companies may want to move away from being BT all-rounders covering each and every market segment. They may split up to specialise—at least to the point where cosmetic and therapeutic indications will be separated. That could be the end of some of the big companies we used to love or to hate.

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