

The birth pangs of monoclonal antibody therapeutics

The failure and legacy of centoxin

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This paper examines the development and termination of nebacumab (Centoxin®), a human IgM monoclonal antibody (mAb) drug frequently cited as one of the notable failures of the early biopharmaceutical industry. The non-approval of Centoxin in the United States in 1992 generated major concerns at the time about the future viability of any mAb therapeutics. For Centocor, the biotechnology company that developed Centoxin, the drug posed formidable challenges in terms of safety, clinical efficacy, patient selection, the overall economic costs of health care, as well as financial backing. Indeed, Centocor's development of the drug brought it to the brink of bankruptcy. This article shows how many of the experiences learned with Centoxin paved the way for the current successes in therapeutic mAb development.

Introduction

On April 15, 1992, the United States Food and Drugs Administration (US FDA) announced that it would not approve nebacumab (Centoxin®), a human IgM monoclonal antibody (mAb) for treatment of Gram-negative sepsis, developed by Centocor, a biotechnology company founded in 1979 to commercialise mAbs. Triggering wide scale dismay among financial investors and biotechnology executives, the news heralded not only possible bankruptcy for Centocor, its shares falling 41% in one day,¹ but also what seemed an obituary for mAb therapeutics overall. What made the shock particularly acute was the fact that the drug had already

received marketing approvals in a number of European countries during 1991 and had been recommended for approval by a FDA Advisory Committee in September 1991. Particularly devastating was the fact that the drug was designed to treat a medical condition known to be a leading and rising cause of death in intensive care units, and for which there was little effective treatment.^{2,3}

While marking a very bleak and painful day for Centocor, in the long-term the drug's failure provided important lessons in the subsequent development, testing and regulation of therapeutic mAbs for the company, as well as the biotechnology industry and regulatory agencies. The event is particularly striking given that today mAb therapeutics form one of the fastest growing and most successful and lucrative segments within the biopharmaceutical sector. The success of this market is exemplified by Centocor's infliximab (Remicade®), a chimeric IgG mAb approved in 1998 for inflammatory and autoimmune diseases, which had global sales of US\$8.1 billion in 2010. As of January 2012, nearly 30 mAb drugs had been approved in the US and Europe, with four of these (Remicade®, Humira®, Avastin®, Rituxan®) among the world's ten best selling drugs.^{4,5}

The history of Centoxin and the aftermath of its termination provides a useful insight into the trials and tribulations not only of mAb drugs, but also the challenges and obstacles faced by executives, physicians and regulators during the formative years of the biotechnological therapeutics industry. At the heart of the narrative are the difficulties the drug posed in terms of

Keywords: monoclonal, therapeutics, gram-negative sepsis, centoxin, ReoPro, centocor, xoma, drug costs

Abbreviations: AR, annual report; FDA, food and drug administration; HS-PP, hubert schoemaker's personal papers; mAb, monoclonal; MSS, meningococcal septic shock; PC, personal communication

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safety, clinical efficacy, testing, financial backing and the overall costs of health care.

Through oral interviews, cited here as personal communications (PC), with key participants and examination of company papers, news sources and published medical articles, this paper traces the origins of Centoxin through to its development, subsequent failure, and the legacy it left for the mAb therapeutics field and the treatment of septic disease. Such a case study aims not only to give insight into the complexities of drug development, but also to show how changes in the understandings of the pathology and treatment of disease affect that process.

Origins of mAbs as Therapeutics

The foundation for the use of mAbs as drugs was laid in the late nineteenth century. In the 1880s, researchers began to explore protective substances (known as antibodies from 1891) found in blood serum, which was understood to confer immunity. Notably, Emil von Behring and Paul Ehrlich based in Berlin, exploited this knowledge for the development of 'serum therapies'. This involved giving patients blood serum (antisera) from animals immunised against the specific diseases. By 1939, serum therapy had become the main mode of treatment against infectious diseases, such as diphtheria and pneumonia.⁶⁻⁹

Despite its success, serum therapy had limitations. First, while effective for some infectious diseases, it was less so for others. Second, the therapy caused adverse effects, such as fever, rashes, joint pains and anaphylactic reactions. Serum therapy was also difficult to administer, cumbersome to use and expensive. Moreover, production was hampered by the fact that it was dependent on antisera drawn from individual animals whose quality of output did not always match that of other animals and whose lifespan was limited. Added to this was the fact that each lot contained a complex mixture of different antibodies (polyclonal antibodies) with a range of specificity and affinities. As a result, each batch required extensive characterization before it could be used. Inevitably this meant lot-to-lot variation in production,

making supply uncertain, expensive and standardisation difficult. With these drawbacks and the rise of sulphonamides in the 1930s and antibiotics in the 1940s, serum therapy was largely abandoned.^{10,11}

While the use of serum therapy began to fade, researchers continued to investigate how the body generates antibodies and the part they play within the immune system. From the 1920s, various scientists began to unravel the chemical structure of antibodies and develop methods to isolate and purify them. Reflecting this interest, by the 1960s scientists had begun to determine the structure of antibodies and their binding mechanism to antigens. Yet, attempts to take this knowledge further were frustrated by the fact that researchers lacked a reliable method to produce a single specified antibody. Some progress in this field was made during the 1960s through the development of new techniques for the fusion of B and myeloma cells and culturing the resulting hybrids, which opened the way to the production of mAbs. By the early 1970s a number of scientists had begun to produce single antibodies with specificity, but these were shortlived and could only be made in tiny quantities.¹²

In 1975, two methods discovered by different groups were found to improve the generation of mAbs. The first was a technique reported by Walter Gerhard and Norman Klinman at the University of Pennsylvania and the Wistar Institute (Philadelphia). This method yielded hybridomas capable of surviving three months.^{13,14} The second, which would come to be seen as a major breakthrough, was that of Georges Köhler and César Milstein, at the Laboratory of Molecular Biology (Cambridge UK), who, in looking to answer a basic research question concerning antibody formation and diversity, developed a process that yielded hybridomas that could survive in cell culture indefinitely.¹⁵ Importantly Köhler and Milstein's work gave scientists, for the first time, access to unlimited quantities of standardised antibodies that were highly specific. Now scientists had the possibility of access to antibodies on an unprecedented scale and a reagent that was more like a chemical than a biological serum product.

Early Steps Toward mAb Therapeutics

Sparking widespread interest within the scientific community around the world, mAbs were quickly utilized for diagnostic purposes and reawakened a dream, first ignited by Ehrlich in 1905, that antibodies could be powerful therapeutic tools or 'magic bullets'.¹⁶ Soon a number of mAbs had been successfully developed for the diagnosis of a range of diseases, including infectious diseases and cancer. Many also began excitedly to explore the therapeutic possibilities of mAbs for cancer, but progress on this front was slow.^{2,17}

Faster advances were made in the transplant field. As early as 1980, reports about the use of mAbs for allogeneic bone marrow transplants and for organ transplantation began to emerge.¹⁷ In 1986, the FDA approved the first mAb drug, muromonab-CD3 (Orthoclone OKT3[®]), to prevent the rejection of kidneys in transplants. Originating from research started in the late 1970s by Patrick Kung at Ortho Diagnostics Systems (a subsidiary of Johnson and Johnson) on immunoregulation and the use of polyclonal antibodies as immunosuppressants in renal transplants, OKT3 marked a milestone for the success of organ transplants.¹⁸⁻²³

As had been observed with serum therapy, however, ~5 to 10% of patients administered OKT3 experienced serious complications, including fevers, thromboses and anaphylactic shock, the incidence of which increased with administration of multiple doses.²⁴⁻²⁶ This was a problem also observed with other mAb therapies being tested in this period that were derived from mouse or rat cells which patients' immune systems saw as foreign material. Such immunogenicity was a major concern given that up to this point mAb production was highly dependent on the use of rodent-derived cell lines. Not only could murine antibodies cause immunogenic reactions, they had short circulating half-lives (15 to 30 h) in humans, necessitating high and frequent therapeutic doses administered by injection. They were also poor at recognizing human receptors.²⁷

There was thus a critical need for new methods to produce mAbs that contained less murine component. Because mAbs

were difficult to produce directly from human cell lines, the challenge was to find an alternative route. Steps toward this goal had already begun before the approval of OKT3. By 1984, several groups of scientists had used recombinant DNA engineering techniques to produce the first 'chimeric' antibodies.^{28,29} Part mouse and part human, chimeric mAbs marked a significant step toward the ultimate goal of reducing the murine portion of genetically engineered mAbs to zero. Thought likely to be less immunogenic and more effective, chimeric, humanized and human antibodies largely replaced murine antibodies as mAb therapeutics.³⁰⁻³²

Gram-Negative Sepsis

Alongside efforts to improve mAb technology and the study of mAbs as cancer treatments and immunosuppressants for organ transplants, infectious diseases were explored as possible avenues for the deployment of mAbs. In particular, Gram-negative sepsis, one of the most intractable and frequently fatal diseases in critical care, attracted attention.

Up to ~1940, sepsis caused by Gram-negative bacteria was fairly uncommon, but it had become a major problem in US hospitals by the 1970s. In 1980, the incidence of Gram-negative sepsis was estimated to be between 10 and 15 cases per 1,000 hospital admissions, causing mortality in 21 to 31% of patients with infections and rising to between 40 and 70% in cases complicated by organ failure. Particularly disturbing was the fact that the incidence of the disease was rising and seemed to coincide with the expanded range and administration of antimicrobial agents, which was followed by the emergence of antibiotic-resistant strains of bacteria, and medical and surgical advances, such as radiography and chemotherapy, that increased the vulnerability of patients to these organisms. Added to this was the difficulty that not all cases responded to antibiotics.^{33,34}

Research in the early 1970s showed that serum taken from patients suffering from Gram-negative sepsis contained antibodies against endotoxin released by Gram-negative bacteria that could diminish the frequency of septic shock and

death.³⁵ Subsequent research, published in 1982, by Abraham Braude and Elizabeth Ziegler, at the University of California, San Diego, showed it possible to reduce the mortality of septic patients with Gram-negative bacteria by 37%, using serum (labeled J5) collected from healthy male volunteers vaccinated with an inactivated strain of Gram-negative bacteria.³⁶ With Gram-negative bacteria known to be the cause of at least a third of septic shock cases, this research gave many people optimism in a field that heretofore had seen little progress.

Representing the first original approach developed for many years, Braude and Ziegler's work ignited a strong impetus for further clinical trials with similar serum therapies and a drive to find more effective treatments for sepsis.³⁷ One of the challenges they faced was the difficulty of making the serum therapy commercially viable. A key drawback was that J5 serum was produced from blood drawn from volunteers and was therefore limited in supply. It also contained polyclonal antibodies that were difficult to standardise and could cause mild toxicity.^{38,39}

Seizing upon mAb technology as a possible way forward, a number of groups were soon tackling the problem. Among those within academic circles were the oncologists Henry Kaplan and Nelson Teng. Based at Stanford University and supported by grants from government agencies, Kaplan and Teng reported in 1984 that they had developed a human IgM mAb (known as A6H4C5 or HA-1A at the time) with 'great promise' for 'both analysis and treatment of Gram-negative bacteremia and endotoxemia'.⁴⁰ Such interest was not confined to the academic community. Between 1980 and 1995, companies were estimated to have spent US\$1 billion in attempts to develop new pharmaceutical agents for sepsis.^{41,42} With sepsis accounting for up to US\$10 billion in health care expenditures annually, the market for such a treatment was expected to reach over US\$300 million by 1990.²

Centocor and Xoma, two biotechnology companies specifically founded to commercialise mAbs, were central participants in this race. At Centocor, the creation of human mAbs against Gram-negative bacteria was given high priority

early on, with the focus on the production process. This, however, was not easy. As Denise McGinn, who began working on the project for Centocor in 1983, recalled, 'I made several human antibodies using B cells isolated from a donated human spleen. In these early days, it was very difficult to generate stable cell lines producing human antibodies from fusions'. By January 1985, Centocor had succeeded in generating their own human mAb for the purpose, but this was abandoned in favor of HA-1A, which had already been shown to protect mice in an animal model of Gram-negative sepsis. (PC, Centocor employees Denise McGinn, David Holveck, Renato Fuchs). Similarly, Xoma opted to in-license edobacomab (also known as Xomen E5), a murine IgM mAb developed by Lowell S. Young at the University of California, Los Angeles.⁴³

Centocor's Development of Centoxin

Licensed by Centocor in early 1986, HA-1A, renamed Centoxin, was one of a number of therapeutic mAb products the company was developing.⁴⁴ The mAb itself had not been easy to obtain, reflecting in part Braude's reluctance to license such a product to a commercial organization. The critical issue for Braude was whether Centocor would be the right company to move ahead with commercial development of the drug (PC, Vincent Zurawski, Centocor employee).

While a promising candidate, the development of Centoxin demanded huge commitment on the part of Centocor and the risks for the program were high. The mAb required extensive purification, formulation and measures for quality control, and the effects of the drug in humans were still unknown. Moreover, Centocor had built a highly competitive and profitable business in diagnostics, but it had little expertise in the development of therapeutics and the development program for Centoxin would require very large capital input. Rather than relying on partnerships and joint ventures, mechanisms that Centocor had successfully used to build its diagnostics business and advance other therapeutic mAbs in its portfolio, Centocor's executives, in part encouraged by Wall Street

advisers and board members, decided that the company should finance the development of Centoxin alone. (PC, Tony Evnin, Venrock Venture Capital investor).

The decision was risky. Up to that time, most biotechnology companies with drugs on the market had done so by licensing the drug to another company for development and marketing. Part of the rationale behind Centocor's decision was the belief that the drug could be a major breakthrough for sepsis and a major blockbuster with potential sales of US\$400 million in the first year. It was also believed that the strategy would give Centocor greater control over the product and larger revenues. Internal development was also believed vital to building the infrastructure that would transform Centocor from its diagnostics base into a globally integrated pharmaceutical company. This was a common ambition for biotechnology companies during this period, inspired in part by Genentech's successful launch in 1985 of somatrem (Protropin®), the first recombinant pharmaceutical product manufactured and marketed by a biotechnology company without the help of partner (PC, Evnin, Fuchs).⁴⁴⁻⁴⁷

Estimating Centoxin would cost at least US\$150 million to bring to market, Centocor's executive plunged into a money-raising campaign led by the company's founder, Michael Wall, and its co-founder and chief executive, Hubert Schoemaker. Between 1986 and 1992, US\$500 million was raised through nine different equity, debt and off-balance sheet financings, secured on the promise of Centoxin and its superiority to Xoma's murine IgM drug, which was also then in development. Much of this money, totaling US\$450 million by 1992, was spent on clinical trials, creation of a European and American sales force of 275 people and construction of two new manufacturing plants, one in the Netherlands and one in the US.⁴⁸⁻⁵⁰ At the insistence of Wall Street advisers, Centocor also made major changes to its management structure, launching a recruitment drive to hire staff from large pharmaceutical companies. Thought vital to advancing the company's skills in drug development and marketing, the arrival of these executives dramatically shifted company culture

toward new management styles, more aggressive marketing and acceptance of much higher expenditures (PC, Centocor employees Bruce Peacock, Pat D'Antonio, Sandra Faragali, Patty Durachko, Ray Heslip, Paul Touhey). Centocor's research and development expenses, for example, increased by 76% between 1985 and 1986.⁵¹

From early on, it was clear that the development of Centoxin would necessitate major investments in manufacturing. Although the company had facilities for making diagnostics, these were insufficient for the production of therapeutics, which required different manufacturing processes and procedures. As early as December 1984, before any therapeutics were in development by the company, Centocor started to build a 40,000 square foot manufacturing facility in Leiden, the Netherlands, aiming to have it running by September 1986. An important factor for locating such a facility abroad was that it would allow Centocor to circumvent US regulations that, before 1986, prevented the exporting of medicines developed within the US but approved elsewhere. Because of the slow pace of regulatory review in the US, Centocor's executives hoped the Leiden manufacturing plant would facilitate earlier approvals, and subsequent sales, of their mAb drugs in Europe. The rationale for locating the plant in Leiden was that, at the time, the city was a leading center in fermentation technology and advantageous tax breaks for building such a facility were available. (PC, Centocor employees: Pedro Tetteroo and Peacock).⁵²

Building a manufacturing plant for mAb drugs, particularly an IgM, was not an easy task. Unlike traditional small molecule drugs, which are synthesized from chemical precursors through well-known reactions used to reproducibly make products, the production of mAbs, like all biotechnology drugs, is reliant on the use of living cells, which can become contaminated, such as with viruses or die. Given these challenges, Centocor's facility required extensive specialized knowledge of cell culture and strict measures to ensure a germ-free environment. Consuming more than 20% of the total original budget, the process of building the center

involved teaching contractors, staff hired to run the facility and regulatory authorities new biotechnology methods. By 1988, Centocor had in place fermentation and downstream processes that would allow the production of commercial quantities of therapeutic mAbs (PC, Tetteroo).⁵³

The manufacturing plant in Leiden was to play a critical role in the development of Centoxin. Development of the IgM mAb required the establishment of a good cell line and appropriate culture conditions for its production. Pedro Tetteroo, Centocor's head of manufacturing in the Netherlands in 1987, recalled that the cell line licensed for production of Centoxin was a 'very lousy cell line', which hindered the isolation of sufficient quantities. In addition, as an IgM molecule, the mAb was less stable than the IgG mAbs that comprised the majority of therapeutic mAbs in development. By comparison with IgG mAbs, IgM is less soluble and easier to denature, which makes it difficult to purify.⁵⁴ While eventually solving this problem, every stage of the manufacturing and scaling up process for Centoxin required new learning, as well as new fermenting equipment and staff (PC, Tetteroo). By 1989, the facility had over 200 staff and a three-shift operation.⁵⁵ In preparation for marketing Centoxin, the company also purchased another manufacturing facility with 90,000 square feet, including a mammalian cell culture plant, in St. Louis (USA), in 1990.⁵⁶

Because of the short time-line for development, many of the measures to develop Centoxin's production were done in parallel with clinical development. Initially, the drug was tested in a pilot study of its safety, pharmacokinetics, immunogenicity and optimum dose among a small sample of cancer patients who did not have Gram-negative sepsis. By 1988 an open label trial of 34 patients who had been diagnosed with the condition had started in six American hospitals. Results, published in early January 1990, indicated that the drug was safe and no patients developed anti-drug antibodies, a problem observed during earlier trials of Xoma's murine IgM antibody.⁵⁷ Thereafter, a 24-center clinical trial modeled on the earlier J5 study was initiated. Patients with sepsis or suspected Gram-negative

sepsis were randomly administered either the drug or a placebo. Strict diagnostic criteria, including a blood test for infection, were used to select patients who were then followed for 28 d or until death. The trial was conducted among a total of 543 patients, including 281 placebo recipients. The results, reported in 1991, indicated that administration of Centoxin reduced Gram-negative sepsis by 39% and reduced mortality by 47% in patients who went into septic shock.³⁸ Another of the drug's trials, started in early 1991, indicated Centoxin helped reduce the mortality of meningococcal septic shock (MSS), a rare but highly fatal form of meningococcal disease, in children.⁵⁸

In September 1989, Centocor submitted a product license application (PLA) for Centoxin to the FDA, which started the regulatory review process rolling. While this was some time after Xoma had filed a PLA for its drug, which had occurred in March 1989, expectations were running high in Centocor for Centoxin. As Hubert Schoemaker and James Walve, the company's newly appointed chief operating officer, wrote in the company's *Annual Report* for that year, the task of getting Centoxin to market had put Centocor at the forefront of writing 'the first chapter in the story of human monoclonal antibodies, powerful new tools which will undoubtedly lead to great advances in medicine well into the next century'.⁵⁹

Validations of the drug were given an extra boost when, in early 1991, the US army ordered a batch of Centoxin at a cost of US\$2,500 a vial from Centocor for administration to soldiers fighting in the first Gulf War.⁶⁰ Further good news came in March 1991 when the European Committee for Proprietary Medicinal Products recommended Centoxin for the treatment of Gram-negative sepsis. Based on this recommendation, Centoxin was subsequently approved in The Netherlands, Britain, Germany and France between March and December 1991. In September 1991, the FDA Vaccines and Related Biological Advisory Committee, although expressing some reservations about the validity of results showing Centoxin increased survival rates in septic shock, unanimously advised FDA approval with restrictive labeling for the drug.^{61,62}

"Centocorpse": Centoxin's Downfall

As the FDA began to deliberate the recommendations to approve Centoxin, Centocor began to receive unsettling news. The first was that initial European sales of the drug were below its predictions. The second was to have even more major repercussions. In late October 1991, a federal court in San Francisco ruled that Centocor's patent for Centoxin infringed one held by its competitor Xoma, whose clinical trials of its IgM antibody for sepsis, for which it had a partnership with the pharmaceutical company Pfizer, had entered clinical testing before Centoxin. This decision came after months of bitter dispute between the two companies that cost Centocor dearly in terms of time and money. It also generated publicity spotlighting concerns about Centoxin's trials so far.^{42,61,63-65}

More bad news followed the patent ruling. In late November 1991, the FDA was alerted to a trial undertaken in specially bred beagles used to assess Centoxin that had been undertaken by the US National Institutes of Health (NIH) Clinical Center's Department of Critical Care Medicine. The study showed the drug to be potentially lethal and unable to protect against sepsis. The results came at the worst possible moment for Centocor who, fearing that such information would be used against them in their legal battle, tried to stall publication of the results. A tempestuous meeting followed between the NIH, the FDA and Centocor in mid-December 1991.^{66,67}

The tension was not helped by the fact that medical practitioners elsewhere were airing concerns about the drug. The most damning came from Jean-Daniel Baumgartner and his colleagues based in Lausanne, Switzerland, who, on testing HA-1A for Merieux Laboratories, a company that had licensed the same mAb as Centocor, had been unable to reproduce the laboratory and animal results originally used to show its usefulness against Gram-negative sepsis. Published in March 1990, Centocor executives had originally dismissed these results.⁶⁸⁻⁷¹ In July 1991, however, Baumgartner and his colleagues wrote a stinging attack on Centoxin in

a letter to the editor of the *New England Journal of Medicine*, concluding,

'Clearly, there is an urgent need for an adjunctive therapy for Gram-negative septic shock. However, it seems premature to rely entirely on a single clinical study before embarking on the large-scale use of such an expensive form of therapy, when there were possible imbalances between the study groups at entry and when the basic understanding of the specificity and the function of HA-1A is incomplete.'⁶⁹

Alongside safety issues, medical practitioners had begun to voice concerns about the high cost of Centoxin.⁷¹⁻⁷⁵ Drawing on the price of the drug established in The Netherlands where it was already marketed, research published by Schulman in a leading American medical journal in December 1991 estimated that the average cost of treatment for each patient with HA-1A in the USA would be US\$5,650, 66% of which was the cost of the drug and the remainder acute hospital care.⁷³ Overall, the study showed that, if given to all patients with sepsis, the drug would cost US\$24,100 per year of life saved. The total cost of treating septic patients could be US\$2.3 billion, of which the drug alone would account for US\$1.5 billion.⁷²

On a positive note, Schulman's research showed that the costs of Centoxin might be two-thirds lower should it be possible to treat only those diagnosed specifically with Gram-negative bacteria. This was particularly significant as sepsis can be caused by a number of different bacteria and only about a third of all patients who suffer sepsis have Gram-negative bacteria. No appropriate diagnostic, however, was available for this purpose. The absence of an accurate means of selecting patients who might benefit from Centoxin was a major disadvantage. While sepsis can kill within a matter of hours, identifying the exact bacteria responsible can take up to two days, which is long after decisions need to be taken to administer a drug such as Centoxin.⁷² The concern this caused was summed up by a letter from clinicians working in Royal Victoria Hospital, Belfast, that was published in December 1991. As they pointed out

'In our intensive care unit Gram-negative organisms were isolated only five times in the past year (September

1990–September 1991) in a population of 500 patients, of whom 40 had severe sepsis. From the data of Ziegler et al. if only 40% of septicaemic episodes prove to be due to Gram-negative organisms then 60% of patients with septicaemia will derive no benefit from Centoxin. For 100 patients with septicaemia this represents a wastage of £120,000 out of a total of £200,000. This wastage will continue until an accurate reliable method of identifying those patients with endotoxaemia becomes available.⁷⁵

Such issues were not confined to Britain where hospitals' budgets were constrained by the National Health Service. Some American hospital administrators were also concerned about the financial implications of Centoxin's use. Duke University Hospital staff, for example, estimated that Centoxin could increase their pharmacy budget between 10 and 40%. In anticipation of FDA's approval of Centoxin, in early 1992 a number of American hospitals, with the help of Centocor, began establishing prescription guidelines for the drug, stressing it be limited to patients with severe sepsis. San Francisco General Hospital, which had large numbers of non-paying patients, was particularly worried about the financial burden of Centoxin. Although other expensive medical technologies had been accepted within the hospital, the tension that emerged over Centoxin was unprecedented. At the heart of the debate was a question of social justice and whether Centoxin would be an appropriate use of resources given its high costs and the difficulty of selecting patients who would most benefit from it.^{49,74-76}

On February 20, 1992 the company suffered yet another setback when the FDA indicated that it needed additional information about Centoxin before it would recommend approval. Triggering shock in the financial community, the tidings sent Centocor's shares tumbling 19%, representing a US\$675 million drop in its market value.^{1,50,64,77,78} Initially believing these problems would be resolved, Centocor's executives faced even worse news three months later when the FDA indicated it would require the evaluation of Centoxin in additional clinical studies before the drug could be considered for

approval. The devastation was great for everyone in the company, as well as investors. As Holveck, then head of Centocor's diagnostics, put it, that day 'everything fell apart' (PC, Holveck). Centocor's press communications officer, Rick Koenig, recalled:

'As if the management did not already know the company was in extremis, Dave [Holveck] presented each of them a framed copy of an editorial [with a] copy of a cartoon depicting the slope of Centocor's stock price as it plunged into a toilet. The title: "Septic Shock"' (PC, Koenig).

Nicknamed 'Centocorpse' by Wall Street, shareholders saw US\$1.5 billion of Centocor's market capitalisation disappear. In the week that followed, disgruntled investors filed six lawsuits against Centocor's executives alleging violation of federal securities laws and called for damages (PC, Centocor employees: Holveck, Faragali, Durachko, Heslip). Sensitive to the calamities of one of its leading companies, the biotechnology industry suffered its own financial aftershock with the news, with many major companies deserting mAbs in development as therapeutics. This was not helped by news that in April 1992 the FDA had withheld the approval of Xoma's IgM drug for sepsis due to insufficient trial data.^{49,79,80}

While the FDA's decision had not killed Centoxin, Centocor's executives desperately needed time and money to rescue the drug. With the future of the company at stake, Schoemaker and Wall immediately plunged into a rescue strategy to stop the company's high cash burn of \$50 million per quarter. Many of the recently recruited pharmaceutical executives and hundreds of sales representatives hired especially for Centoxin's launch were let go, and Schoemaker and Wall began looking for a suitable partner for support. (PC Paul Touhey, Centocor employee; Stelios Papadopoulos, Paine Webber Investor). As assets, they had other promising candidates in Centocor's pipeline, and the fact that some pharmaceutical companies, such as SmithKline Beecham, were very keen to obtain Centoxin despite its problems (PC, JP Garner, SmithKline Beecham). By July 1992, Centocor had secured a licensing agreement with Eli Lilly whereby Centocor would receive

US\$100 million upfront from Lilly to help develop Centoxin in exchange for a 5% stake in the company, an unprecedentedly large payment for the time. In the event that Centoxin failed, Lilly also agreed to pay a further US\$25 million toward the development of abciximab, an antibody-based cardiovascular drug that Centocor was developing simultaneously.⁸¹ In the months that followed, Lilly and Centocor worked closely on a new trial for Centoxin that was initiated in June 1992. Six months later, however, the trial had been abandoned and European sales of Centoxin had been halted because interim data from the trial indicated unexpectedly high mortality among patients who did not have Gram-negative bacteremia.⁸²⁻⁸⁵

Lessons

In the aftermath of Centoxin's failure, many theories were put forward in both the investor and medical communities for what had gone wrong. One explanation was that the pressure to transform Centocor into an integrated pharmaceutical company had driven the company to adopt new and more aggressive management practices that were ultimately destructive and spending patterns that were unsustainable. Another was the competition with Xoma. Because Xoma completed clinical development and submitted an application with the FDA for its mAb drug several months ahead of Centocor, some company executives had unwisely put pressure on the FDA. As Wall later explained 'When you're losing \$50 million a quarter, every week [your drug is] not on the market is crucial. So you call the FDA every day'.^{48,49,85}

A critical issue that arose during FDA's review of Centoxin's PLA was that half-way through the first trial two of its executives had seen unblinded interim results handled by an independent committee, which had allowed the potential introduction of bias into the trial's results. What was particularly worrying for the FDA was the fact that these executives, and some statisticians who had participated in reviewing the interim data, 15 mo into the study had been involved in changing the trial's protocol's clinical endpoints from 14 to 28 d (PC, Jay Siegel, FDA regulator, October 2010).^{49,86}

A major problem for Centocor was that it was a new company with substantially less capital and experience at gathering preliminary data necessary for designing appropriate clinical trials than well-established pharmaceutical companies. As a biotechnology-derived drug, Centoxin also posed different challenges than those of traditional pharmaceuticals. Moreover, the drug was designed as a treatment for a disease that was still poorly understood, had little consensus in how it might be defined and for which there was relatively little experience because the incidence of sepsis rose sharply only after the 1970s. Other confounding factors were the facts that the spectrum of microorganisms (e.g., Gram-negative and Gram-positive bacteria and fungi) responsible for sepsis was not consistent, the disease was difficult to diagnose prior to administration of a drug, and sepsis patients were often gravely ill from other diseases. Attempts had been made in 1989 to establish a simple definition of sepsis that included the source of the infection, but clinical signs of sepsis were frequently present in patients whose blood lacked measurable levels of bacteria. Further complicating the picture was the fact that, as a disease, sepsis is a complex entity that affects virtually every physiological regulatory mechanism within the body (PC, Siegel).⁸⁷⁻⁹² In many ways, the problems Centocor executives faced were characteristic of the development of antibacterials in general, but, at the time, Centocor had little experience with drug development.

When designing the Centoxin trial, Centocor's executives also entered what was largely uncharted territory regarding trial design, including selection of appropriate endpoints, entry criteria, and use of concomitant medications. The difficulty was the Centocor team tried to analyze multiple subpopulations within the trial and used various definitions for the endpoint. Multiple approaches were also taken to handle patients who were lost to follow-up. All of these factors complicated analysis and interpretation of the results. On top of this too little statistical adjustments had been done to take into account the different levels of other medications, such as antibiotics, given to patients within the trial. The inadequacies

exposed in the Centoxin trial design were not only a lesson for the company, but also for FDA officials who themselves were new to the manufacturing, clinical testing and regulation of mAbs. The only other such therapeutic, OKT3, had been approved in 1986 for a much narrower and well-defined indication. Tellingly, all subsequent agents, including Xoma's drug, developed for sepsis failed when tested in second confirmatory trials (PC, Siegel, Schaible).^{93,94}

While painful, the lessons learned from the development of Centoxin for sepsis were to prove useful to Centocor in going forward. Where this became apparent was in the on-going trial of Centoxin in children with MSS. The advantage of the trial, continued among 269 patients until 1995, was that the drug was directed toward a much narrower and more defined population than studied for sepsis and the disease's clinical diagnosis was easily possible at the bedside owing to its characteristic skin hemorrhages. Part of the rationale for continuing the trial, which was conducted in both the US and Europe, was that the effects of the drug on mortality would be more easily measured than had been possible for the other indications studied to date, and that, unlike adults with sepsis, children with MSS were less likely to have underlying diseases that could confound results. Another asset was that children presenting with the disease tended to have higher incidences of Gram-negative bacteremia than adults with sepsis. Although the drug was well-tolerated, the trial failed to show Centoxin had any significant affect on MSS patients. While further clinical investigation could have been pursued, investigators from the trial predicted that the complex and multi-factorial process involved in treating sepsis meant that no single treatment agent directed at only one stage of the disease would have an appreciable clinical benefit.^{83,95}

Out of the Ashes

While Centoxin's failure marked the first of a number of commercial disappointments in the sepsis field and management of the disease continues to be elusive, study of the drug provided critical biological insights into sepsis as a disease and brought

vital knowledge about the development of subsequent mAb drugs to Centocor (PC, Harlan Weisman, Centocor employee).⁹⁶ Such knowledge helped lay the foundation for the company to gain regulatory approval of later drugs.

In December 1994, the FDA approved Centocor's cardiovascular drug abciximab (ReoPro[®]), which was then the second mAb drug to gain the authority's approval. ReoPro (also known as 7E3) was first developed as a basic research tool used to define the biochemistry involved in platelet physiology and pathology. Licensed by Centocor in 1986, much of the early development and testing of ReoPro was undertaken and sponsored by Centocor, boosted by the support of Lilly in the wake of the failure of Centoxin. On arrival at Centocor, clinicians knew the mAb could help prevent blood clots, but how it might be deployed clinically remained uncertain. Originally murine in origin, Centocor's scientists quickly set about converting the mAb into a chimeric antigen-binding fragment through genetic engineering, an innovative move for the time, thereby making it safer and more commercially viable. Careful planning was then put into its clinical testing. Believed possibly useful for a number different clinical situations, including prevention of blood clotting in people undergoing or about to undergo a heart attack, Centocor's clinical investigators prioritised its development as a means of preventing acute ischemic complications in patients undergoing coronary angioplasty, a common procedure to unblock coronary arteries. Importantly, the effects of the drug would be easy to define and measure (PC, Centocor employees: Harlan Weisman, Denise McGinn).^{97,98}

Leaning on Lilly's long expertise of successful drug approvals and learning from its mistakes in the handling of Centoxin, Centocor's investigators were mindful to apply the highest possible standards to the scientific planning of ReoPro's clinical trials and for handling interim results. With the future of Centocor at stake, no chances were to be taken this time. Much to the relief of Centocor's team, in early 1993 it became clear from the results from the first trial that ReoPro had achieved its primary endpoint and that the company finally had a viable drug. (PC, McGinn).

The positive news, however, was only the beginning of the complex clinical development and regulatory review process, which was undergoing changes in the US. ReoPro faced stiff scrutiny in the US, and was expected to be presented to a FDA advisory panel that had never previously handled or approved a biologic drug. Careful not to repeat their mistakes with Centoxin, Centocor's executives were especially mindful to maintain a collaborative relationship with the regulatory authorities, e.g., by following FDA's advice to supply them with only relevant material. In the case of Centoxin, the company had supplied too much paperwork, which in itself had complicated approval (PC, Centocor employees: McGinn, Michael Melore, Thomas Schaible).

Submitted for review in 1993, ReoPro took just ten months to be approved by the European regulatory authorities and 12 mo by the US FDA. These approvals came through in December 1994. This was particularly heartening given that many within the biotechnology industry had lost their faith in mAb therapeutics and few believed such a drug had merit or commercial application.⁹⁹ ReoPro's approval not only marked a critical milestone for Centocor, but placed mAbs firmly on the therapeutic map. Moreover, the company had shown that mAbs could be used successfully for treating acute conditions. The first therapeutic product ever to receive simultaneous US and European approvals, ReoPro's development phase was the fastest of any cardiovascular drug to reach the market. In December 1995, ReoPro's marketing potential was further boosted when clinical trials showed that it was effective for unstable angina, broadening its potential market to more than 1 million patients. More cheer was to follow when research in 1996 showed the drug to be cost-effective, an issue that had plagued Centoxin.^{100,101}

Conclusion

As the impact of ReoPro began to be felt within the clinic, marketing applications for more mAb therapies as treatments for other diseases were submitted

to regulatory authorities. By 1997, two mAbs had reached the marketplace for cancer, Centocor's drug edrecolomab (Panorex[®]), which was briefly marketed in Germany, and Idec Pharmaceutical's drug, rituximab (Rituxan[®]). This was followed in August 1998 by the approval of Centocor's infliximab (Remicade[®]). Initially approved for Crohn disease, Remicade is now a blockbuster drug used for numerous autoimmune and inflammatory disorders, including rheumatoid arthritis. Remicade's approval not only hailed a major breakthrough for previously poorly understood or untreatable diseases, but proved that mAbs could be viable treatments for chronic diseases. Poignantly, Centocor had initially investigated Remicade as a treatment for Gram-negative sepsis.¹⁰²⁻¹⁰⁴

With mAb therapeutics becoming an increasingly important part of health care, the trials and tribulations of Centoxin are a powerful reminder that the path to the market for such drugs is never inevitable or straightforward. As the case of Centoxin shows, the development of such drugs poses major questions not only about manufacturing and clinical testing and the costs involved, but also about the very nature of disease pathology and appropriate therapeutic options. For the pioneers involved at the dawn of therapeutic mAb development, this was to be a journey characterized by substantial risks and personal sacrifices. Some idea of the roller coaster ride this involved can be gleaned from the experience of Harlan Weisman, who headed Centocor's development of ReoPro. As he recollected,

'I joined [Centocor] in January 1990 and at the time the price of the stock was just under \$20. Based on the high hopes placed on Centoxin, the stock went to \$50 to \$55 a share by January 1991. I remember it well because it was my one-year anniversary, and I was awarded stock, which counted as income by the IRS. But when my taxes were due in 1992, the stock had fallen to \$5.50 and I had to pay taxes at \$55. My taxes due were higher than the value of the shares I owned. I had to borrow money from the company to pay my taxes.'¹⁰⁵

The story of Centoxin and the subsequent rise of mAb therapeutics is a

powerful reminder of the complex inter-relationships needed between academia, industry and regulators to develop mAbs as therapeutics, and the degree to which their future rests on advancing our understanding of the disease process, drug development and regulation, as well as the volatility of the financial market.

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