Omalizumab, the innovative biologic that disrupted the market of the treatment of allergic diseases

Trabajo Fin de Grado
Grado en Bioquímica
Curso 2022-2023

Autor: Irene Pérez Herranz
Tutor: Dr. Jerónimo Carnés Sánchez

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EXECUTIVE SUMMARY

Omalizumab, the blockbuster monoclonal antibody anti-IgE that revolutionized the market by the disruptive innovation that supposed more than 20 years ago. This biological drug changed the paradigm of the treatment of allergic diseases, particularly severe allergic asthma and chronic spontaneous urticaria. It opened up a new alternative world of possible treatments, covering the clinical unmet needs of asthmatic patients and creating value for patients who do not respond well to traditional medicines (small-molecules). Its efficacy and safety have been demonstrated in numerous clinical trials and Real-World Evidence. These observations have favoured the life cycle management of the product for new applications, including nasal polyposis and food allergies. However, it is no longer the only biological on the market for the treatment of these pathologies, so how is it possible that after so many years it is still a blue ocean product?

Biologics represent the upcoming of treatments, as they treat diseases in a safer, precise and more effective and personalized way. They represent the future of our health.

2. Innovation in Health and Pharma

2.1. Definition and concept

Innovation can be defined as a novel creation that produces value. It is about action and creating results. There are two types of innovation, incremental and disruptive. Incremental innovation involves the continuous improvement and development of existing products, rather than the creation of entirely new ones. This type of innovation typically involves making small but significant changes to an existing product to enhance value. Incremental innovation can be an effective way for pharmaceutical companies to maintain their market position, extend the life of their existing products, and differentiate themselves from competitors. However incremental innovation may not address significant unmet needs, as it focuses on optimizing existing products rather than developing new ones. Then disruptive innovation comes into play.

Innovation is, particularly relevant in the pharmaceutical industry. Innovation, is necessary to solve problems and improve people´s lives. It is essential as new diseases appear, change or evolve. There are diseases that do not yet have cures or effective treatments, and which affect a significant number of the population. There are constantly new demands, unmet needs, and competitors, which require new strategies and business models. Making innovation inevitable.

2.2.What is disruptive innovation in Pharma?

Disruptive innovation is a strategic pillar in Pharma industry, is the development of new treatments or technologies that fundamentally change the way healthcare is delivered or that create entirely new markets. Disruptive innovations often emerge from outside the traditional pharmaceutical industry. They offer new approaches to drug discovery, development, delivery, or pricing, based on consumer needs. It is transforming an idea into a new and effective solution. Disruptive technologies and innovations cause drastic market changes (1).

Disruptive innovation is one of the fundamental mechanisms by which the quality of our lives has improved and increased. The disruptive innovation model generates the most value, and

carries the most risk. They often require significant investment and a long-term view of drug development, new regulatory frameworks or reimbursement models to be established.
However, major changes are generated by this model.
According to the model, disruptive innovations often originate in a niche market, where they are initially seen as inferior and are not taken seriously by established players in the industry. However, as the technology or product improves, it gradually gains acceptance and eventually disrupts the existing market by replacing the established players' offerings. Disruptive innovation focuses on the impact on the market, rather than on the novelty introduced. The impact that produce in the market can lead to; the change of the structure of the market, create new markets or make existing products obsolete. However, it is not immediate to classify a disruptive innovation until long after it has been introduced. This makes it very difficult to collect data through research surveys (2).
In the pharmaceutical industry, disruptive innovations can come in the form of new technologies, treatments, or business models that challenge traditional approaches to drug discovery, development, and delivery.

The disruptive innovation model is explained in the following figure, it shows the contrast product performance trajectories (red lines showing how products or services improve over time) with costumer demands trajectories (the blue lines showing customers' willingness to pay for performance) (3). As incumbent companies introduce higher-quality products or services (upper red line) to satisfy the high end of the market (where profitability is highest), they overshoot the needs of low-end customers (3). This leaves an opening for entrants to find footholds in the less-profitable segments that incumbents are neglecting (3). Entrants on a disruptive trajectory (lower red line) improve the performance of their offerings and move upmarket and challenge the dominance of the incumbents (3).

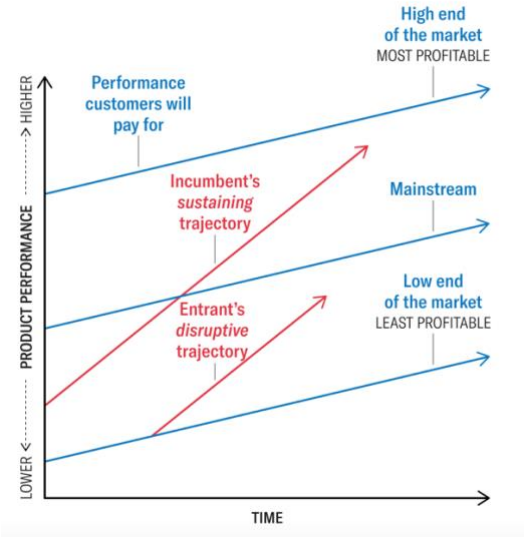

Figure 1. The disruptive innovation model by Harvard Business Review (3).

Disruption describes a process whereby a smaller company with fewer resources is able to successfully challenge established incumbent businesses (3,4). Specifically, as incumbents focus on improving their products and services for their most demanding (and usually most profitable) customers, they exceed the needs of some segments and ignore the needs of others (3,4). Entrants that prove disruptive begin by successfully targeting those overlooked segments, gaining a foothold by delivering more-suitable functionality, at a lower price (3,4). Incumbents, chasing higher profitability in more-demanding segments, tend not to respond vigorously (4). Entrants then move upmarket, delivering the performance that incumbents' mainstream customers require, while preserving the advantages that drove their early success. When mainstream customers start adopting the entrants' offerings in volume, disruption has occurred (3,4).

Is disruptive innovation an optimal business model in Pharma?

With this innovation model, a company can create a blockbuster, and grow immeasurably in the market, generating extraordinary profitability and benefits. On the other hand, it can lose millions, but that is what risk is all about.

This requires a high investment, the R&D costs required for disruptive innovation are very high. However, innovating in the pharmaceutical industry means taking risks, as the one that took Novartis with Omalizumab years ago that turned out to be a successful case originating a revolution in medicine and changing the paradigm of allergic diseases.

3. Biologics as the center of innovation in Pharma.

3.1. Importance of biological medicines and their benefits.

What is a biologic medicine?

According to the European Medicines Agency (EMA), a biological medicinal product is a product that contains one or more active substances synthesised or derived from a biological source (5,6).

They are obtained from living organisms such as yeast, human tissues, animal cells or bacteria. They are innovative drugs produced by biotechnology and genetic engineering (by recombinant DNA technology) from genetically modified cell lines. Unlike conventional or generic drugs, biologics have certain advantages.

Biological drugs suppose a great revolution on the pharma and health industry. They are currently being used to treat a variety of medical conditions for which no other treatments are available or effective. They are new therapies directed at specific biological targets. These include diseases such as autoimmune diseases, infectious diseases and neoplasms. Biologics offer new approaches and more effective methods of treating the patient. These products are capable of addressing the disease from a molecular point of view, identifying what is characteristic of that disease. To do this, they signal a target.

The importance of this new type of drug is increasing exponentially and more clinical trials are devoted to demonstrate the efficacy of this technology, thanks to its greater performance and better results in the treatment of chronic degenerative diseases.

According to the Precedence Research, and as Figure 2 shows, the worldwide asthma treatment market size was estimated at $25.8 billion in 2021 and is expected to reach over $30.1 billion by 2027, addressed to grow at a compound annual growth rate (CAGR) of 2.6% throughout the period 2021-2027 (7).

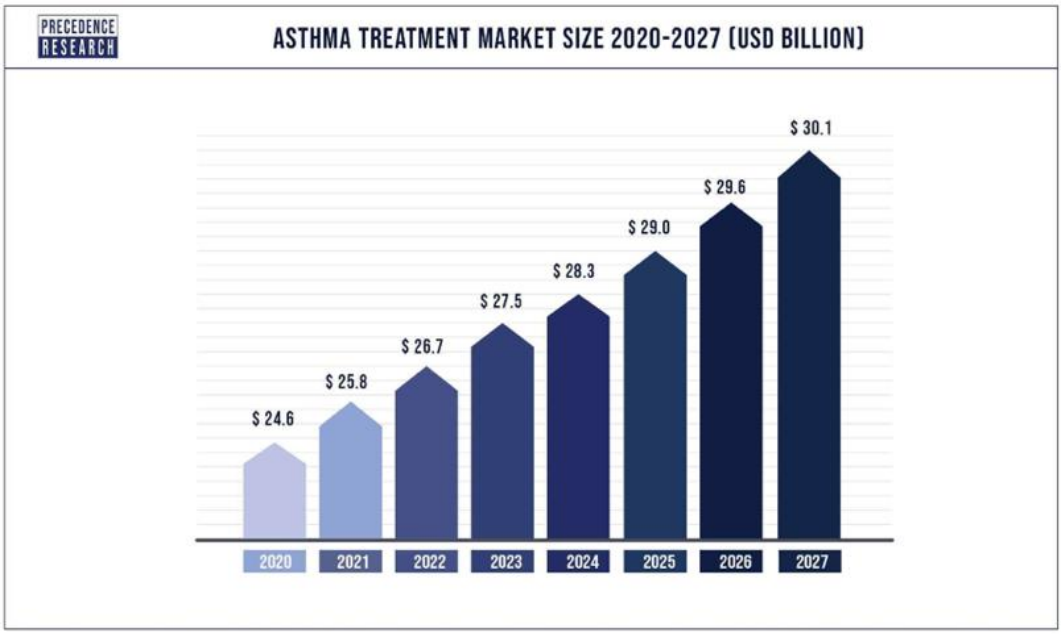

Figure 2: Asthma treatment market size between 2020 and 2027 in USD billions. By Precedence Research (7).

Additionally, according to Precedence Research, the global biologics market was estimated at US$ 366.43 billion in 2021 and it is expected to hit over US$ 719.84 billion by 2030 (7).

3.2. Advantages and limitations compared to conventional medicines.

The major differences between biologics and small molecules are listed in Table 1 (8).

Biologics	Small molecules
Produced by living cell cultures	Produced by chemical processes
High molecular weight	Low molecular weight
Complex, heterogeneous structure	Well-defined structure
Strongly process-dependent	Mostly process-independent
Not entirely characterizable	Completely characterizable
Unstable	Stable
Immunogenic	Nonimmunogenic

Table 1: Biologics Vs. Small molecules

Biological drugs have several advantages over small molecules or conventional products. Their targeted approach, long-lasting effects and the potential for personalized medicine, make them an important option for patients with a wide range of severe conditions. They also can have long-lasting effects in the body, biologics do not need to be administered

as frequently as conventional drugs. In the case of Omalizumab, it has to be administered subcutaneously every 2-4 weeks.

Biologic drugs as innovative products

One of the principal advantages of a biological drug is that they create and add value. Biologicals are innovative drugs that contribute to sustainability and they have revolutionized the field of medicine and leading to significant improvements in the treatment of various diseases.

They are designed to target specific proteins, cells or pathways involved in the physiopathology underlying the specific disease. Some of these drugs work in a similar way to proteins produced by the body itself, so that when administered to a patient they are capable of suppressing the symptoms of the disease and prevent or delayed its progression. This targeted approach can result in a greater efficacy and less side effects compared to traditional drugs. The security, quality and efficacy of biologic products are the same or even better compare to a small molecule (9).

Regarding the unmet needs, biologics have opened up new ways for treating untreatable conditions, such as certain types of cancer and autoimmune diseases. Since some biological drugs, such as vaccines and immunotherapies, stimulate the body´s own immune system to fight the disease, rather than directly target it.
In the case of asthma, the main advantage of biologics is the capacity to reduce the number of asthma exacerbations, which includes ER visits, hospitalizations, and the need for oral steroids. Biologics have been found to improve asthmatic patients' quality of life (7).

Main constrains of Biologics

The development of a biosimilar product has certain disadvantages compared to conventional drugs.

- Their development requires greater investment, since their research and manufacture are more complex. This makes them more expensive to produce, and their availability is more limited. Their high cost can make them unaffordable for many patients, limiting

the access to these live-saving treatments. Although the price is expected to drop as demands grows.

- About the side effects of biological drugs, patients must be monitored while receiving these medications, mainly during the first doses. They can produce allergic reactions and infections (because they reduced the Ig E, that provides protection against parasites) in a relatively small number of patients. Nonetheless they do not have as many side effects as traditional medicines.

- As regards the immunogenicity, some biological drugs can stimulate the immune system to produce antibodies against the drug, which can reduce its effectiveness over time.

3.3. Types of biological products and medicines.

There are different types of biologicals, according to its nature, including: mRNA, DNA or recombinant protein vaccines; serum and blood products; allergenic vaccines and extracts for allergen immunotherapy; recombinant or chimeric proteins; monoclonal antibodies; gene therapy and fermented products and reagents used for in vitro diagnostics.

- Conventional vaccines of mRNA, DNA, proteins or attenuated agents, that stimulate the immune system to produce and immune response and develop immunity to a specific disease.
- Recombinant or chimeric proteins are developed by introducing specific genes into the genetic material of the host, which manufactures these proteins for therapeutic use, producing a passive immunization phenomenon in the patient.
- Blood derivatives are obtained from the plasma of healthy human donors by fractionation and subsequent purification processes.
- Recombinant allergens, proteins that are manufactured by introducing genetic material into microorganisms and are the agents responsible for sensitization, triggering an immune response.
- And finally, monoclonal antibodies (mAb), immunoglobulins modified and designed to adhere with high specificity to an antigen and stop a pathological process. mAb against selective targets are one of the most promising and effective biological products. This

is why mAb are a key factor in drug development and in personalized, precision medicine.

3.4. Monoclonal antibodies (mAb).

3.4.1. Historical background.

As a historical event, Paul Ehrlich in 1900 propose his theory of "side chains". He claimed that the cells of the organism produced receptors, side chains, which were able to bind to bacterial toxins by molecular complementarity, so that when a cell is in danger it produces an excess of such side chains and become circulating antitoxins, capable of acting against bacterial toxins (5).

What is the origin of mAb?

Its history begins in 1975, date in which there was an important event in the discovery of these drugs, the development of hybridoma technology, by Khöler and Milstein, for which they received the Nobel Prize in Physiology and Medicine in 1984.

The first therapeutic monoclonal antibody produced using this technology was Muromomab (anti-CD3, T cell), of murine origin. It was approved by the FDA in 1986 in transplant patients for the treatment of rejection. However, the use of murine monoclonal antibodies had important limitations, due to their non-human origin. Their short half-life in plasma and the production of human antibodies against murine chains, caused significant adverse effects, limiting their clinical use (5).

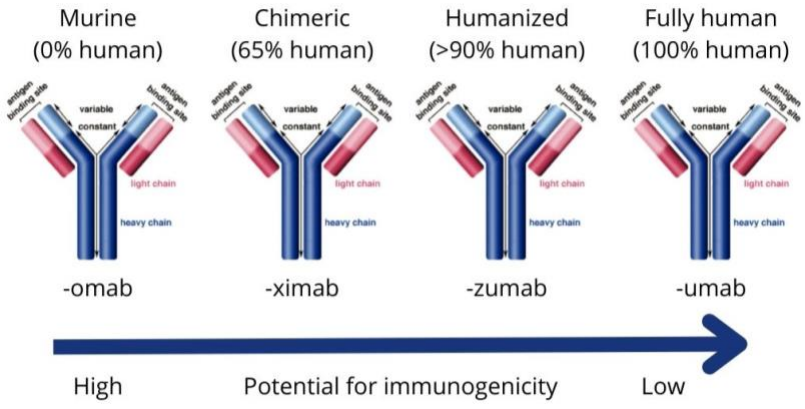

Figure 3. Classification of monoclonal antibodies.

In order to avoid these problems, genetic engineering techniques were developed to obtain second-generation mAb or recombinant mAb (Figure 2), in which fragments of the murine antibody were changed by human proteins.

Initially, chimeric monoclonal antibodies were obtained, in which the Fab region is of murine origin while the crystallizable fraction Fc is of human origin. Chimeric monoclonal antibodies contain approximately 65-90% of human chain and the suffix is

-ximab. The first chimeric monoclonal antibody, rituximab (anti CD20, B cell), was approved in 1997.

Subsequently, humanized mAb were obtained, in which the Fc region remains of human origin and the Fab region is partially human and partially murine. They contain approximately 90-95% of human chain and the suffix is -zumab. The first humanized antibody, daclizumab, was approved in 1999.

Omalizumab is a humanized mAb (anti-IgE) and nowadays there are wide variety of cytokine-targeting biologics for allergic diseases listed in Table 2.

Antibody source	Nomenclature (suffix)	Example	Function
Humanized	zumab	Omalizumab	anti-IgE
		Reslizumab	anti-IL-5
		Mepolizumab	anti-IL-5
		Benralizumab	anti-IL-5R
Fully human	umab	Dupilumab	anti-IL-4R (IL-4/IL-13)

Table 2. Cytokine-targeting biologics for allergic diseases.

3.4.2 Production and quality control of monoclonal antibodies.

<u>Therapeutic mAb production techniques.</u>

mAb are modified immunoglobulins, specifically designed to act against specific targets, with the aim of interrupting a specific pathological process, stimulating a certain cellular action or diverting a cellular mechanism towards a pathway of interest (5).

The structure of the mAb should be explained regarding its mechanism of action, biological activity and stability. It should involve a discussion on the suitability of the product's

immunochemical properties, the affinity, isotype, allotype and cross-reactivity. Also, the importance and integrity of effector function.

With respect to the production of mAbs, they should be in accordance with relevant guidelines, particularly with "Production and Quality control of medicinal products derived by recombinant DNA technology" (3AB1A), and the ICH guidelines Q5A (for viral safety), Q5B (expression constructs) and Q5D (for cell substrates) (10). The different approaches to obtained mAb should be carefully examined and justified with regards quality, safety and efficacy.

mAb can be produced by recombinant DNA (rDNA) technology, hybridoma technology, B lymphocyte immortalization or additional technologies (10).

3.4.2.1. Hybridoma technology.

This technology was an important breakthrough, since it allowed to obtain specific antibodies capable of recognizing a single epitope or antigenic determinant and producing them in an unlimited way.

The procedure begins with the immunization of a mouse with the antigen of interest, then B lymphocytes are extracted from the spleen of the animal and fused with myeloma neoplastic cells that gives them the ability to multiply indefinitely. In this way, a fusion cell is obtained, a hybridoma. Next, the hybridomas capable of producing the desired antibodies are selected and the expansion of the clone of greatest interest occurs. Finally, the antibodies obtained are purified.

An unlimited source of antibodies produced by a cell clone is obtained, which derive from a single B lymphocyte, and which are therefore identical and specific to individual epitopes (Figure 4) (5).

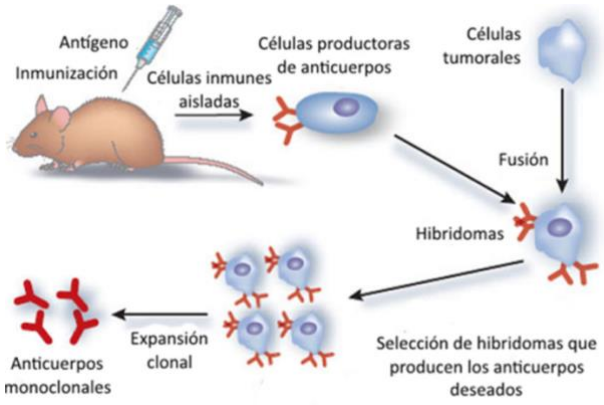

Figure 4. Schematic representation of obtaining mAb using hybridoma technology (5).

Production of therapeutic monoclonal antibodies

The industrial manufacturing process of mAb consists of two fundamental stages explained in Figure 5:

1. The processing or upstream phase (small-scale production).
2. The transformation or downstream phase (large-scale production).

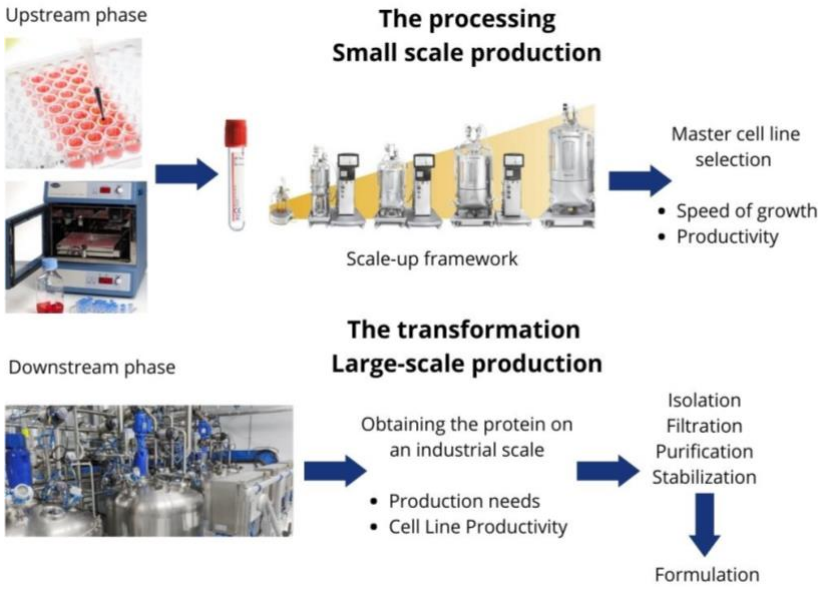

Figure 5. Fundamental stages of the industrial manufacturing process of mAb.

The elaboration phase begins with the culture of the cells, which will be responsible for producing the therapeutic protein. These cells are grown on a small scale, in petri dishes, which contain the culture medium needed for the cells to grow(11). Once the cell line is acquired, it is cryopreserved in several vials to generate a cell bank (9). When the manufacturing procedure of a batch is going to be executed, a vial is thawed from the cell bank and cell culture is began in a flask with a small volume of culture medium (9). During the scaling procedure, cells are transferred subsequently to larger containers.

The cells with greater growth capacity are grown in bigger volume equipment and the production rate of the protein of interest and its quality are evaluated (9). This phase is critical, since it must end with the selection of the master cell line, which is the one that will move to the last stage of the process. (5). The selection of the master cell line is carried out based on:

- The growth rate (concentration of cells/unit of time) in the final system.
- The productivity of the cell line (amount of protein produced by each cell).

The next stage is the transformation, the downstream phase or large-scale production. Is the scale of manufacture needed, which will be set on by the demands (based on the market volume) and the productivity of the cell line (9). The mAb is then isolated from the cells to be subsequently put through successive filtration and purification procedures (chromatography and ultrafiltration) (9). These procedures are also a crucial part of the manufacturing process, as they can have an extremely critical impact on the overall economics of the process based on the achieved performance. At last, the product is formulated in accordance with current specifications (5).

The production is complex because smaller differences can affect the cells and alter the proteins, that is the reason why precise controls are essential to guarantee the quality and duplicability of the final product. It is necessary to control variables such as: oxygen levels, temperature, pH, [nutrients], etc. In addition, tests should be carried out to check for the absence of contamination with other microorganisms (5).

4. Omalizumab as an innovation model.

4.1. The disruptive innovation of Omalizumab.

Allergic asthma is a prevalent disease with a complex physiopathology. It represents a medical challenge and a serious health burden. Multiple studies showed that allergic asthma is associated with greater healthcare costs and the impact of allergic asthma on a patient's quality of life is important. Allergic asthma is defined as a respiratory obstructive disease caused by the allergic sensitization to environmental allergens (extrinsic asthma), with a clinical correlation between exposure and symptoms. It is a disease typically mediated by IgE which trigger the allergic response when, attached to the surface of the effector cells, recognizes the offending allergens. Allergic asthma is one of the most common chronic pathologies and ranges from mild to severe (12). Severe allergic asthma (SAA) constitutes approximately 5% of the total asthmatic population. Traditional treatments often involve the use of inhaled or oral steroids and other medications with potential side effects and less efficacy. The consumer needed a revolutionary medicine that did not focus on palliating the symptoms of the disease.

Omalizumab, supposed a revolution, by redefining the paradigm of asthma treatment. It opened up a new alternative world of possible treatments.

Why is Omalizumab a disruptive product?
Omalizumab is considered a disruptive innovation in the field of allergy and immunology because it represents the change of paradigm from traditional treatments for asthma and also hives. Disruptive innovation has provided an alternative to these pharmacological treatments, to small molecules, which in allergic diseases are not enough.

Omalizumab was the first biologic drug approved for the treatment of asthma. Its efficacy has been demonstrated in many different studies in reducing the frequency and severity of asthma exacerbations and improving lung function in patients with SAA. Monoclonal antibodies may treat asthma patients with higher efficacy and safety than inhalers, and avoid peaks of severe crises. In consequence the use of monoclonal antibodies to treat asthma is growing dramatically. It has also been shown to be effective in treating chronic spontaneous urticaria (CSU), a condition that can be difficult to manage with traditional therapies. The development of Omalizumab paved the way for other biologic drugs that target specific components of the immune system to treat a range of conditions, including autoimmune diseases such as rheumatoid arthritis.
Overall, the development and use of Omalizumab represents a major advancement providing a more targeted and effective approach to treating allergic diseases and improving the quality of life for patients.

4.2. Change of paradigm. The biologics world.

Despite the availability of several treatment options for patients with chronic diseases, conventional medicines fell short in the treatment of these pathologies. There was an unmet need that Novartis identified and covered with this biological drug, marketed by the brand name Xolair®. The active substance, a mAb named as Omalizumab works by targeting and binding to immunoglobulin E (IgE), responsible for the allergic response. By binding to IgE, it prevents from triggering the allergic response, by down-regulating the high-affinity IgE receptors (FCεRI) and regulating mast cell degranulation thereby reducing the free IgE. Xolair® reduces the release of mediators over the allergic inflammatory cascade (13).

Omalizumab is used for patients with moderate to severe asthma who do not respond well to traditional asthma medications. During the years, Omalizumab has gained strong evidence of safety and efficacy in the treatment of severe asthma not controlled by step- up therapy and for other chronic diseases. Biologics for asthma management opened up new market opportunities.

Over the years, Novartis increased the value of Omalizumab by marketing the drug to a broader patient population worldwide. They discovered that it could treat other pathologies too, by reducing the IgE levels leading to the obtaining of additional approvals. This resulted in an increasing demand in the market of this product. That is the life cycle management, that will be explained later on.

Furthermore, Novartis increased the value of Omalizumab after receiving the European Commission (EC) approval for self-administration of Xolair® prefilled syringe, allowing patients with SAA and CSU to administer their own treatment (13).

The development of Omalizumab, the biologic that revolutionized the market, is an example of successful innovation in the pharmaceutical industry. It is also an example of how scientific research can lead to the development of new and effective personalized treatments for patients with chronic conditions. Biological drugs have significantly improved the treatment of complex diseases and they have saved a lot of lives. Currently, mAbs hold the lion's share of the biologic market sales. They remain the largest technology class within the biologic pipeline (14). They represent new therapeutic horizons and therefore the future of our health.

And beyond omalizumab?

Years later, the mechanism of asthma was fully elucidated. If IgE trigger the allergic reactions, it was demonstrated that asthma reactions are mediated by pro-inflammatory T2 response, mainly meditated by IL-4, IL-5 and IL-13. In addition, others Il, including IL-25 and IL-33 were also responsible. The era of mAbs for removing proinflammatory T2 cytokines such as Il-5, Il 4 and Il13 has begun.

Patients with severe symptoms may experience significant limitations in their activities and it also can have significant phycological impact.

Current treatments are focused on step-up approaches according to severity (12). In addition, a clinical evaluation of the phenotype in patients with severe asthma, to optimize therapy with more personalized strategies. This is attribute to the variability of clinical, biological and functional characteristics of patients with asthma, which has led to the emergence of phenotyping. Patients with severe asthma share clinical and pulmonary function characteristics,

however, there are biological markers that differentiate them (12). Studies have shown the existence of at least five phenotypes of severe asthma, grouped according to clinical, biological, lung function and airway inflammation characteristics (12). This has allowed the development of new therapies, new therapeutic mAbs, more specific and directed to the phenotype presented by the patient, which will later be mentioned.

5. Patent right and intellectual properties of Omalizumab

5.1 Concept

Intellectual property (IP) is a major milestone for protecting innovation and huge investments. Although IP is always important in any business, in the pharmaceutical industry and biotechnology companies is even more relevant because the development and launching of a product to the market needs 10-12 years and hundred-thousands millions of euros. Patents allows them to protect their inventions and discoveries. It is essential for the pharmaceutical industry and biotechnology companies, as it allows them to protect their innovations and to maintain a competitive advantage in the market, excluding competition. Patents give them the exclusive right to commercialize the process or product for a certain period of time.

IP ensures a financing mechanism and constitute a system for innovation (15). As it allows companies to recover the R&D costs necessary to create new products and treatments.

This is because during the time that the patent is active, the competition cannot bring to market another product equal to that of the patent, so the only one that will be available in the market will be the one that the company with the patent has developed. This means that, excluding the competition, the company can recover everything invested in the development of that product through sales. So, a company, recovering that investment, can reinvest in the development of another product or process and continue innovating.

5.2. The patent of Omalizumab.

The patent for Omalizumab was registered by Genentech and published in 2001 under the patent number US6329509, giving rise to a family of patents, all of them expired, the last in 2018. Since 2018, several generic drug manufacturers have developed biosimilar versions of Omalizumab and obtained marketing approval from regulatory agencies.

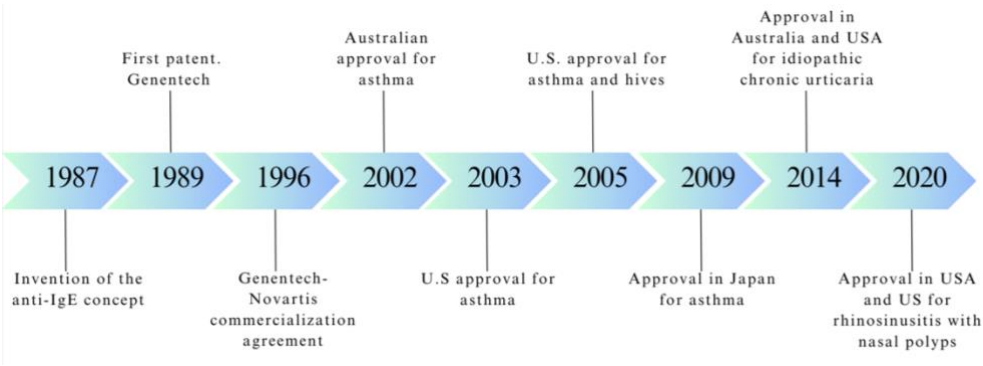

Figure 6. The history of Omalizumab.

The first authorization was for severe asthma in adults, subsequently its use in children has been authorized, and has been extended to other pathologies such as chronic urticaria or nasal polyps, that is the life cycle management of this biologic.

Tanox/Novartis developed a chimeric anti-IgE derived from a mouse mAb and a humanized anti-IgE, which was studied in Phase I and II clinical trials. Later, Omalizumab emerged at Genentech. In 1996, the two programs were combined and Omalizumab was chosen to continue product development, as Figure 6 shows.

The product is currently marketed by the two companies that initiated the development of the product, Genentech (subsidiary of F. Hoffmann-La Roche Ltd of Switzerland) and Novartis, as well as by the Indian company Cipla Ltd. Omalizumab biosimilars are marketed by the companies Generium (Russia) and Reliance Life Sciences Pvt Ltd (India). Another 16 companies around the world are developing Omalizumab biosimilars. In addition, the patent families in which Omalizumab appears in the title/abstract and which are currently active are 559.

6. About the drug development process.

6.1. The Drug Development Phases.

The drug development process is very complex and with a high risk associated, it requires 10-12 years and hundreds-thousands millions of euros.

In each of the steps in Figure X there is a significant risk that the compound does not meet the necessary requirements to proceed with the process. In such case, the significant investment that the company made could be lost.

Figure 7. The Drug Development Process.

The Drug Development phases, summarise in Figure 7, begin with the discovery of a new drug by basic science research and target identification. In Step 1, the discovery and development process, thousands of compounds may be potential candidates, however after early testing, only a small number of compounds look promising to be developed into medical treatments (16). Further studies are made in order to gather information on how the compound is absorbed, distributed, metabolized and excreted (ADME), about its mechanism of action and the potential benefits, the side effects, is effectiveness comparing to similar drugs and the best way to give the drug (16).

Step 2, Preclinical Research, previous to testing a drug in people, researchers must detect whether it has the potential to cause serious harm. The 2 types of preclinical research are in vitro and in vivo studies. They provide precise information about the toxicity levels and dosing, using the good laboratory practices (GLP). After testing, researchers review the information and decide whether the drug should be tested in humans (16). Then the lead optimization and scale-up process for manufacturing are done and the Investigational New Drug Process (IND) must be submitted before beginning clinical research, it is an application to the FDA. The FDA review team has 30 days to review it and approved it or not.

Step 3, Clinical Research refers to studies, or trials, that are done in humans. The developers design the clinical study considering what they want to accomplish for each of the different Clinical Research Phases. Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies as Figure 8 shows (16).

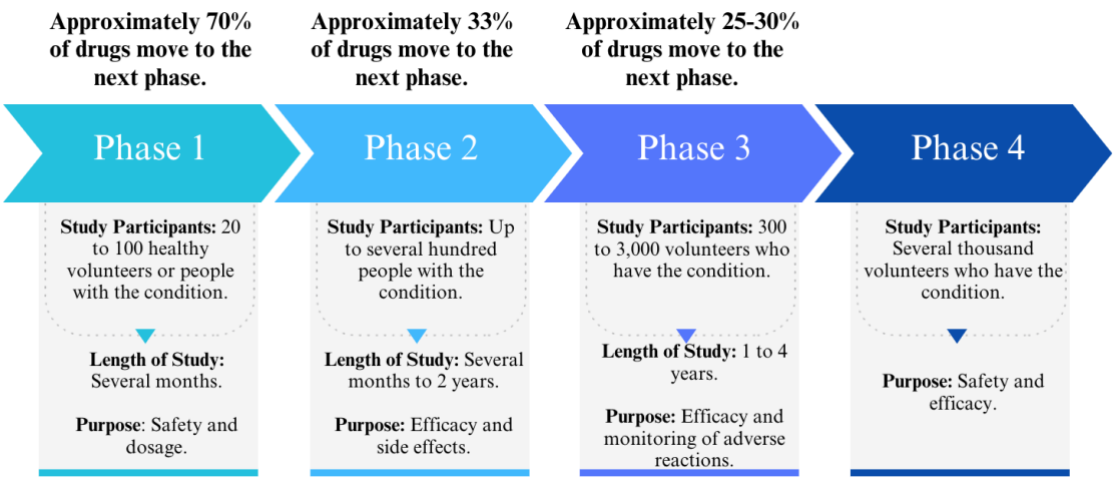

Figure 8. Clinical Research Phases with their characteristics and probability of succeed and move to the next phase.

The developer is responsible for informing the review team about new protocols, as well as serious side effects seen during the trial. After the trials ends, researches must submit study reports (16).

Step 4, Regulatory Phase, the FDA review team examines all the submitted data on the drug and makes a decision to approve it or not. The developer has evidence from the preclinical and clinical research that the drug is safe and effective, so the company file an application to market the drug (16). A New Drug Application (NDA) is made by the developers, it must include reports on all analysis and data, drug abuse information, safety updates, patent information, proposed labeling and directions for use (16).

Lastly, The Post-Market Drug Safety Monitoring. Although clinical trials provide the important information on the drug´s efficacy and safety, the accurate vision of a product´s safety evolves over time. In addition, developers must file a supplemental application if they want to make changes from the original NDA, changes in formulation, labeling or dosage strength must be approved by FDA before (16). Furthermore, FDA conduct routine inspections of the drug manufacturing facilities, to make sure that the developers are following the Good Manufacture Practices (GMP).

6.2. About Omalizumab development phases.

In 1996 Novartis and Genentech combined their resources and Omalizumab began its development. It took more than 15 years of clinical development and approximately $1000 million until it was finally approved by the USA in 2003 and by the European Union in 2005 for the treatment of patients with moderate/severe asthma of allergic origin (17).

After having carried out the necessary studies for the development of Omalizumab, Xolair®, of Novartis Pharmaceuticals, it was seen that the best route of administration was subcutaneous (18).
Xolair® should be stored under refrigerated conditions 2º-8ºC (19). It is recommended to be used after reconstitution (within four hours), as there is no way to preserve it in the formulation (19). Vials should be preserved from the straight sunlight.

Efficacy

The safety and efficacy were demonstrated for adolescents and adults (12 years of age and above) with moderate to severe persistent asthma, whose symptoms are not controlled with inhaled corticosteroids. In addition, for the treatment of CIU who persist symptomatic even with antihistamine treatment (18). The efficacy of omalizumab was first demonstrated in randomized, double-blind, placebo-controlled studies. In these studies, Omalizumab significantly reduced exacerbations, asthma symptoms, emergency room visits, and improved patients' quality of life (18).

A succession of toxicology studies were conducted to demonstrate the safety of Omalizumab. Since omalizumab does not bind to mus musculus IgE, the mouse was chosen to determine high dose nonspecific toxicity(18). The preclinical toxicity evaluations were conducted with the cynomolgus monkey because omalizumab has approximately a similar affinity for IgE purified from cynomolgus monkey serum (0.19 nM) as for human IgE (0.06 nM) (19). Furthermore, the monkey is an exaggerated version of atopy, as baseline serum [IgE] are more significant in monkeys, in contrast with the observed atopic individuals enrolled in the clinical studies (18). As a consequence, monkeys had elevated levels of omalizumab-IgE complexes than would be contemplated. This acute and multiple-dose toxicity studies revealed that Omalizumab produced no adverse clinically relevant effects at serum concentration of drug. An amount of up to 250mg/kg induced thrombocytopenia (18).

After these studies, the dosage considered for asthma treatment with omalizumab is 150 to 375 mg administered subcutaneously (SC) every 2 or 4 weeks. Doses and frequency are determined by serum total IgE level (IU/mL) and body weight. The dosage contemplated for treating CIU patients is 150 mg or 300 mg, administered SC every 4 weeks (18).

About the clinical pharmacology, the pharmacodynamics in clinical studies with asthma patients and Omalizumab, the unbound IgE (serum free IgE) were decreased in a dose dependent process within 1 hour after the first dose and conserved between doses. In CIU patients treated with this mAb, led to a dose-dependent reduced of serum free IgE (18). The highest suppression of free IgE was observed three days after the first dose. The pharmacokinetics after subcutaneous injection, Omalizumab is absorbed with an average absolute bioavailability of 62% (18). The pharmacokinetics are linear at doses greater than 0.5 mg/kg. Tissue distribution studies in monkeys indicated no specified uptake of this mAb by any organ or tissue. About the elimination of omalizumab, it involves the IgG clearance proceeding, also by its binding and complex formation with its target ligand, IgE. The elimination includes the degradation in the liver reticuloendothelial system (RES), besides it is excreted in bile (18). When they study the elimination of the complexes Omalizumab-IgE, in mice and monkeys, this were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance.

In the clinical studies for asthma treatment with Omalizumab, it was absorbed slowly, reaching peak [serum] after an average of 7-8 days, with an apparent volume of distribution of 78 ± 32 mL/kg (18). Omalizumab serum elimination half-life averaged 26 days in asthma patients. In CIU clinical studies with this mAb, the peak [serum] was after 6-8 days, and the half-life omalizumab serum elimination averaged 24 days (18).

The clinical trials of Omalizumab for the efficacy and safety were demonstrated in 4 randomized, double blind, placebo-controlled, multicenter trials (18). Furthermore, additional data from 2 open-label supervised studies in moderate to SAA (studies 5 and 6) were done (18).

- Studies 1 and 2 were identical designed for the evaluation of asthma exacerbations. Both trials enrolled 1.071 atopic patients between 12-76 years old with moderate to severe persistent asthma for at least one year. The number of exacerbations was reduced in patients treated with Xolair® compared with placebo (18).
- In Study 3, the safety and corticosteroid sparing effect of omalizumab was demonstrated in 246 patients with severe allergic asthma requiring daily treatment with high-dose

inhaled corticosteroids (fluticasone ≥ 1000 micrograms /day) and long acting beta 2-antagonist (18).

- In Study 4, the efficacy and safety of omalizumab were showed in 405 patients from 12-75 years old with allergic asthma and allergic rhinitis (18).
- The open-label controlled studies (studies 5 and 6) in moderate to SAA, were to evaluate the depletion of exacerbations and the improvements in the quality of life with Omalizumab, in rhinitis and asthma patients, comparing to placebo (18). Study 5 was supervised for 52 weeks in 312 adult and adolescent patients with uncontrolled allergic asthma (18). It was created as an efficacy investigation of Omalizumab, it evaluated the number of asthma related incidents (the needed of oral corticosteroid; work or school absent days due to asthma; emergency room visits, or unscheduled physician visits due to asthma) (18) .

Safety

The information obtained in the clinical trials about the adverse reactions most commonly observed among patients treated with Xolair® included; injection site reaction (45%), viral infections (24%), upper respiratory tract infection (19%), sinusitis (16%), headache (15%), and pharyngitis (10%). In addition, anaphylaxis has occurred after the first dose of Xolair® in premarketing clinical trials and post-marketing reports, the frequency attributed to Xolair® use was estimated to be 0.2% of patients. Respecting the helminth infection amount in the overall clinical studies, it was less than 1 in 1,000 patients (18).

6.3.Real World Evidence (RWE).

Omalizumab is the first mAb that was internationally approved as a personalized treatment alternative for patients with moderate to SAA uncontrolled, despite treatment with high-dose controller medications (20,21).

After almost two decades of the use of Omalizumab, the effectiveness and safety has been well-demonstrated in the real-life practice of patients receiving it. The Real-World effectiveness of Omalizumab for the treatment of allergic diseases; SAA, chronic idiopathic urticaria (CIU), nasal-polyps and food allergies, has been long study in real life. As it was approved for the

treatment of asthma 2 decades ago, there is more safety and efficacy data on omalizumab as a treatment for SAA. Patients receiving Omalizumab had statistically significant reductions in asthma symptoms and severe exacerbations. Add-on, omalizumab consistently reduced the oral corticosteroid use, the health care resource utilization (decreasing the amount of medical care visits and hospitalizations) and school/workdays absenteeism, improving the quality of life of patients receiving it (20,21). One meta-analysis included 86 real-life studies of patients with SAA treated with omalizumab for more than 16 weeks. The global treatment efficacy evaluation (GETE) was good/excellent in 77% of the patients at 16 weeks, and in 82% of patients at 12 months.

Biomarkers

Several biomarkers have been recognized to predict the efficacy of omalizumab with higher responses rates from the target patients, such as: total IgE levels, T-helper-type-II (Th2) inflammation biomarkers such as blood and sputum eosinophils and the fraction of exhaled nitric oxide (FeNO). Those results guided the European Respiratory Society (ERS) to recommend, as biomarkers, the FeNO and blood eosinophil count, with a high value for the boost response to omalizumab (20).

Overall the results of Xolair® administration on the quality of life of patients receiving it, by applying the Juniper's Asthma Quality of Life Questionnaire, provided a clinically significant greater improvement in asthma over placebo (18). These were demonstrated in 4 asthma domains of the Asthma Quality of Life Questionnaire (AQLQ), including: activities, symptoms, emotional function and environmental exposure (18). A synopsis of the amount of patients that achieved clinically upgrading in the AQLQ is included in Table 3.

Study number	Omalizumab %	Placebo/Control %	p-value
1 (28 weeks)	66	55	<0.05
2 (28 weeks)	67	57	<0.05
3 (32 weeks)	52.3	35.7	0.004
4 (28 weeks)	78.8	69.8	0.002
5 (32 weeks)	71.8	43.2	<0.001

Table 3. Clinically significant improvement in the quality of life (18).

The proven efficacy and safety of omalizumab, made this mAb, subcutaneous injection, safe to self-administer at home, not having to travel to the hospital or medical center, saving costs and time to the healthcare system and to the patient.

7. The model of omalizumab.

7.1. Life cycle management (LCM).

The efficacy and safety of Xolair® has been demonstrated in numerous clinical trials and real-world studies over these two decades. After its approval and marketing, initially, for the treatment of SAA, it was observed that by blocking IgE, there were also other allergic diseases that could be treated with this mAb, this is the life cycle management of omalizumab. Basic research and real-world evidence address the efficacy of Omalizumab in chronic induced urticaria (CIU), in rhinosinusitis with nasal polyps and the off-label ongoing investigation for food allergy.

7.1.1. Chronic spontaneous urticaria.

Chronic spontaneous (idiopathic) urticaria (CIU or CSU) is a complex disease, defined as the occurrence of wheals and/or angioedema, for more than 6 weeks. It affects 1-2% of the total population and it represents an important burden that affects patient´s quality of life. CIU is associated with psychiatric comorbidities, causing depression or/and anxiety, in addition, it interferes with routine daily activities, leading to an indirect cost approximately of 244$ millions (in the USA) because of the medication costs and work absenteeism expenses (22).
The mechanism leading to CIU are not completely understood, but it is thought that CSU is a chronic inflammatory skin disease in which various inflammatory cells and mediators are involved. The treatment is based on a first line non-sedating anti-H1 antihistamines at recommended doses. If there is no improvement, the antihistamine dose increased up to 4 times. However, about 50% of the patients are not controlled with antihistamines (22).

For many years, it was though that IgE was not a major factor involved in the pathogenesis of this complex disease. But it was demonstrated that omalizumab present a clinical efficacy in patients with CIU. Omalizumab is the only biologic drug approved by regulatory agencies as

an add-on therapy for the treatment of adolescent and adult patients with CIU who remain symptomatic despite optimized H1-antihistamine therapy (22). In double-blinded placebo-controlled studies and in real-world studies, the effectiveness of Omalizumab have been confirmed. Recommended doses of 150 or 300 mg are given by a subcutaneous injection every 4 weeks (22). In some patients, a delayed response of up to 6 months is observed (22). The proposed mechanism of action of this mAb in chronic urticaria treatment is because of the reduction of [IgE] and a decrease of FcεR1 receptors on skin mast cell membrane, although additional mechanism of actions has been suggested. However, there are still some issues that interfere with omalizumab use, mainly its high cost, the relapses once the treatment is suspended and the not established optimal duration (22).

7.1.2 Nasal Polyposis treatment.

The majority presentation of chronic rhinosinusitis (CRS) with or without nasal polyposis (NPs) are considered as type II inflammatory diseases of the upper airway. These inflammatory conditions are identified by infiltration of eosinophils, basophils and mast cells, that are recognized by the expression of cytokines related with T-helper 2 effector cells (IL-4, IL-5 and IL-13) (23).

Current treatments involved combinations of medical therapies with nasal saline irrigation, antibiotics, combinations of topical and systemic corticosteroids or even surgery. Nowadays, these approaches come up with a long-term benefit and are less expensive than biologics (23).

Omalizumab may be efficacious in the treatment of NPs because of the elevated level of tissue expression of IgE. This correlates with the severity of the disease. Omalizumab treatment was related with clinical significantly lower total nasal endoscopic polyp score. However, following studies are essential to evaluate and address the cost-effectiveness of biologics in these conditions and measuring the adverse impact of these disorders on the quality of life (23).

7.1.3 Treatment of Food Allergies.

Food allergy prevalence is increasing, at an estimated rate of 1.2% per decade (24). It affects 8% of children and 10% of adults in the USA. For example, peanut allergy had a prevalence of 2% among children in a 2011 US survey (24). So, the health care costs associated with food

allergies are growing, because of the increase of the hospitalizations rates and emergency visits (24).

Currently, there is no FDA-approved biologic treatment for use in food allergy, however, omalizumab is been studied as monotherapy and as adjuvant in the treatment of food allergies, in conjunction with oral immunotherapy (OIT) for peanut, cow´s milk and hen´s egg (24). However, omalizumab as monotherapy has a nonspecific effect on food allergy. But, the combination of omalizumab with oral immunotherapy result in a faster desensitization and reduction in the inflammatory response throughout up-dosing, by boosting the threshold dose of food protein necessary to provoke a reaction. The goal of using omalizumab as an adjuvant to oral immunotherapy is to enhance the tolerability, by reducing the side effects of oral immunotherapy dosing (24).

Omalizumab was accepted by the FDA in 2018 to promote its future approval as a treatment of severe food allergic reactions (24). This is the off-label indication of omalizumab. Off-label refers to the use of this previously authorized biologic, for different conditions, not contemplated in the summary of product characteristics.

Omalizumab requires more clinical trials to demonstrate its performance in the treatment of food allergies and in the development of long-lasting and long-term tolerance (24).

7.2. Omalizumab in the global market.

Novartis created 20 years ago a blockbuster for asthma treatment that had worldwide sales of more than 1$ billion.

Omalizumab, active substance of Xolair®, which first hit the U.S market in 2003, had its niche in asthma patients who do not respond to conditional treatments and with moderate-to-severe persistent allergic asthma. It was commercialized for a price around $1360. In 2011, it was marketed in Spain, as a prefilled syringe solution for injection (1 ml) for a price of 436,99 euros. Xolair® indication for the treatment of SAA is approved in 90 countries around the world, 10 less than for the indication of CIU (25).

The niche market of Omalizumab has been expanding as more indications have been approved or are under study. Furthermore, due to the increasing prevalence of CIU, SAA and other allergic conditions worldwide. Globally, the prevalence of allergic diseases is rising fast. An amount of 8-10% of the global population experience from one or more allergic condition, from mild rhinitis to anaphylaxis or severe asthma (26).

The basis for allergy prevalence in the population is mainly genetic and environmental predisposition. Host factors such as; sex, race, age and heredity (the phenomenon of allergic diseases has a strong genetic basis) influence the predisposition of an individual to suffer from an allergic condition. In addition, environmental factors; passive smoking, pollution, dietary habits and infections have an important role in the development of allergic diseases (26).

The incidence of asthma in 2020 by The Lancet global burden of disease (GBD), indicated that the USA, Africa, India and Indonesia have higher prevalence of asthma.

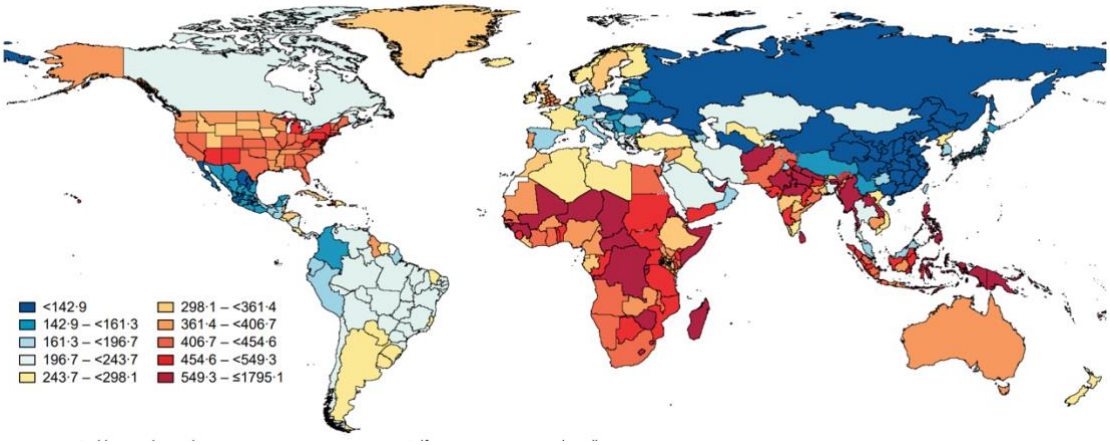

Figure 9. The Global prevalence of asthma by The Lancet GBD (27).

Compared to urticaria, where the highest incidence is in Russia, Canada, Greenland, some countries in Europe, Australia, India and in the countries of the Persian Gulf.

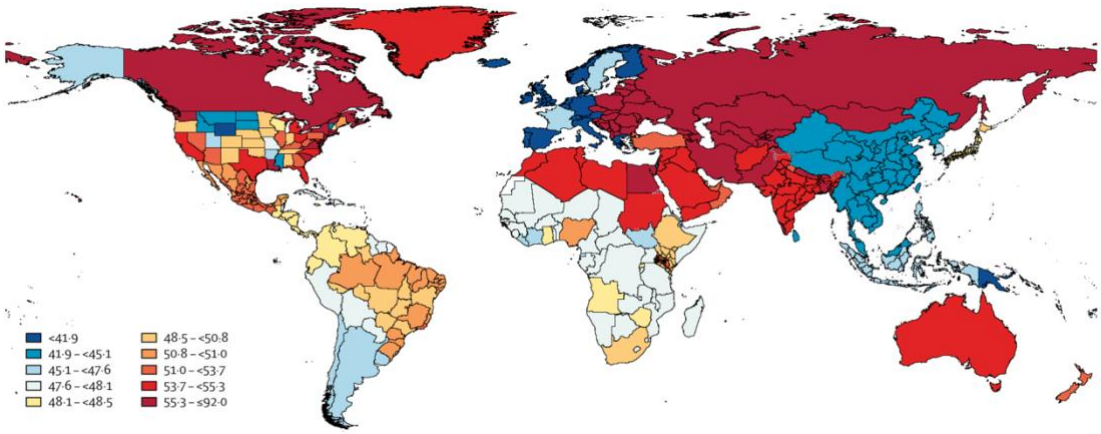

Figure 10. The Global prevalence of urticaria by The Lancet GBD (28).

In the United States and Europe, the availability and use of omalizumab is higher, this is because its use is restricted by the high price of this drug and by health insurance or health coverage in some countries. However, the prevalence of allergic diseases, especially asthma and urticaria, are higher in other countries as shown in figures 9 and 10 but the health system of these countries cannot cover the high cost of this biological.

Competitors

Competition plays a very important role in the market of Omalizumab, which after the patent expired in U.S in June 2016, other companies developed and commercialized mAbs for the treatment of allergic diseases. Sales of Xolair® have been challenged by fast-growing competitors that enter this field.

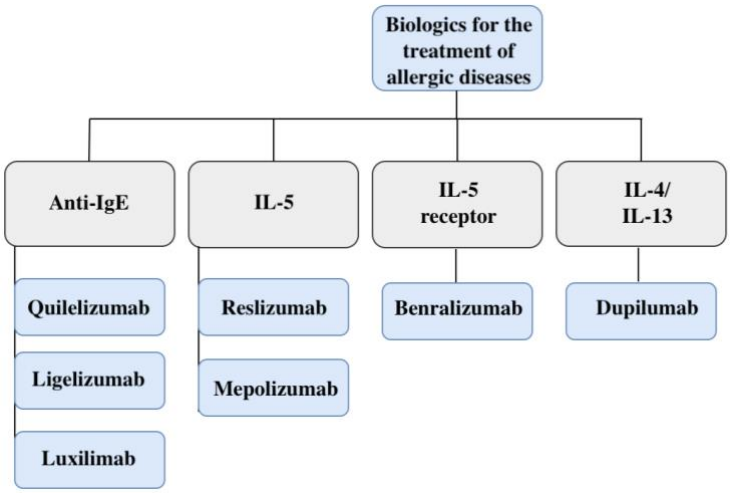

Figure 11. Biologics approved or under study for the treatment of allergic diseases.

Table 4 summarises the information on other biologic drugs approved and marketed, with the date of FDA approval, the company that develops it and the commercial name. Its mechanism of action and indications will be discussed in section 8.

Biologic	FDA approval	Company	Commercial name
Benralizumab	11/2017	Kyowa Kirin Co Ltd	Fasenra®
Dupilumab	03/2017	Sanofi and Regeneron	Dupixent®
Reslizumab	03/2016	Teva Pharma	Cinqair®
Mepolizumab	11/2015	Gsk	Nucala®

Table 4. Summary table of the biologics for the treatment of allergic diseases.

Therefore, what competitive advantages does Omalizumab have over other biologics?

To analyze the market situation of Omalizumab, I performed a SWOT analysis. It is a strategic analysis that evaluates the product allowing the identification of; the strengths, weaknesses, opportunities and threats.

Figure 12. SWOT analysis of Omalizumab.

Although there are other biologic drugs approved for the treatment of SAA and CIU, Omalizumab remains an important therapeutic option due to its well-established efficacy and safety profile, with 20 years of experience in the market. In addition to all the data obtained from the clinical trials and the Real-world Evidence studies.

Biosimilars also have a role in this market. They are FDA-approved biologic drugs that are comparable to another drug, the parent drug. They are usually cheaper than biologicals, however, nowadays there is none approved for the treatment of allergic diseases.

How is the market for biologics that treat allergic diseases in Spain?

The prescription trends of Biologics for SAA in Spain; omalizumab, mepolizumab, Reslizumab and Benralizumab, are shown in Figure 13. We can observe that Omalizumab remains the most

prescribed and used drug in Spain for the treatment of SAA, followed by mepolizumab. We can also observe that the use of these biologics is greater in the Canary Islands and in the south of Spain. This corresponds to the higher prevalence of allergic diseases in these places. The use of mAb as a treatment for allergic conditions in the Canary Islands amounts to 20.3%, while in the south of Spain it corresponds to 19.4%, followed by the east area with 13.8% and central area with 13.4%, lastly, the north area of Spain with 11.5% of prescription trends of this drugs.

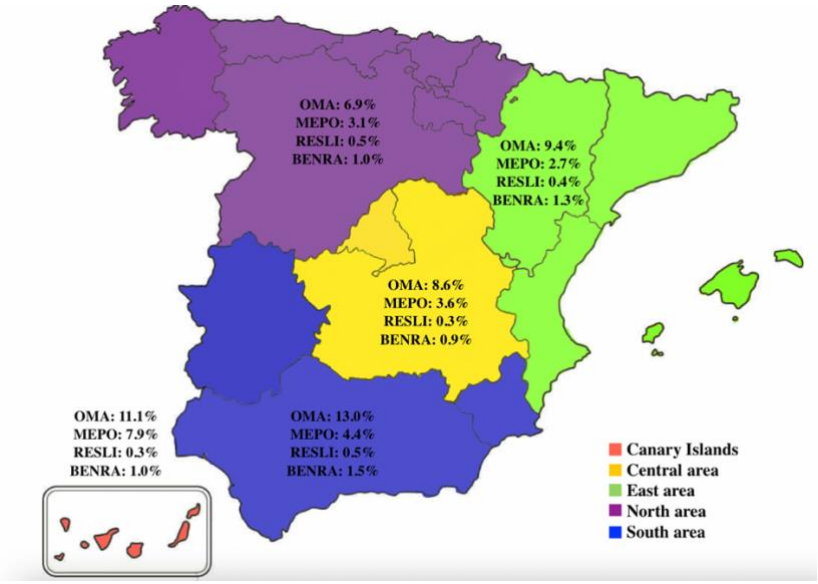

Figure 13. Monoclonal antibody treatment for SAA in Spain by the International Congress of the Iberian Allergology Societies SEAIC-SPAIN 2023.

Omalizumab opened up the market of biologics and provided the chance to selectively interfere with particular steps in the immune inflammation cascade, achieving almost complete control of asthma and chronic urticaria (29).

The revolution of the biologics is still advancing, there are drugs in progress and others newly marketed (29).

8. Next generation products

8.1.Other biologics for the treatment of allergic diseases.

In section 7, the other biologics used in allergy have been mention and described in a simplified manner. In this section, the mechanism of action and the characteristics of the most common biologics used in allergy will be described.

Table 5 summarizes the main milestones of biologics used in allergy ordered by year of authorization. It included the target, the authorization year with the clinical indication, the patent year and the patent expiration year in every place.

Biologic	Company	Target	1º Authorization	Patent	Patent expiration
Mepolizumab	Gsk	IL-5	2015 SAA from age 6	1996 (US5683892)	2021 Except Cyprus (2028)
Reslizumab	Teva	IL-5	2016 SAA from age 18	1997 (EP0765392)	2015 Europe 2021 USA
Dupilumab	Regeneron	Receptor IL-4 α	2017 eosinophilia or moderate to severe asthma	2008 (US2008160035)	2032 Europe 2040 USA 2041 Japan
Benralizumab	Kyowa Kirin	Receptor IL-5α	2017 severe eosinophilic asthma	2005 (US7718175)	2024 USA 2025 Europe and Japan
Tezepelumab	Amgen	TSLP	2018 patients with severe asthma	2009 (US2009238823)	2028 Japan 2029 USA 2033 Europe
Tralokinumab	Medimmune	IL-13	2018 patients with severe asthma	2007 (US2007128192)	2024 Europe 2031 Japan 2028 USA

Table 5. Most common biologics used in allergy with its main milestones.

The mechanism of action of these biologics is summarized in Figure 14.

- Mepolizumab, a humanized murine IgG1k mAb (29). It selectively targets the α-chain of IL-5, preventing its binding to IL-5 receptor α (IL-5Rα), which is expressed on the surface of basophils and eosinophils (29). As a consequence, eosinophil differentiation, activation and growth are inactivated (29). The approved dose is subcutaneous injection 100 mg every 4 weeks.

- Reslizumab, a recombinant humanized IgG4k mAb able to block IL-5 and interfere with its functions (29). With a similar mechanism of action to mepolizumab. The only difference is the way of administration, Reslizumab has an intravenous way of administration. This way seems to provide a more robust pharmacologic effect and a further reduction of airways eosinophilia. This mAb is approved at the dosage of 3 mg/kg every 4 weeks (29).

- Dupilumab, is a fully humanized mAb able to bind, with higher affinity and specifically, the α subunit of the IL-4 receptor, shared by the IL-4/IL-13 type II receptor complex (IL-4α/IL-13Rα) and to inhibit the signal of both cytokines (29). This inhibition is able to suppress the inflammatory response, the chemokine and cytokine cascade induced by their activity (29). The dosage of this subcutaneous injection is 200 or 300 mg every 2 weeks.

- Benralizumab, a fully humanized IgG1k mAb, that selectively binds the IL-5 receptor α epitope and interferes with IL-5 signalling, independently of the ligand presence (29). IL-5 Receptor α is expressed on eosinophils and basophils, but also in their progenitors in the bone marrow (29). This mAb depletes IL-5 Receptor α expressing cells through antibody-directed cell-mediated cytotoxicity (29). It also has an afucosylation on the oligosaccharide core, so it significantly enhances the affinity for human Fc γ Receptor IIIa, mainly expressed in NK cells, so NK contribute to the depletion of eosinophils in the bone marrow and blood, and to almost complete depletion in tissues and sputum (29). The recommended dose of this subcutaneous injection is 30 mg every 4 weeks for the first 3 doses, and then every 8 weeks.

- Tezepelumab is a humanized mAb blocking TSLP, cytokine that expresses the innate immunity activation, by preventing the interaction with its receptor complex. TSLP is produced by the epithelium and it regulates dendritic cell functions, activates B cells, regulates Th2 cytokine production and polarizes the differentiation of naïve T cells into mature CD4 T cells (29). The recommended dose of this subcutaneous injection is 210 mg every 4 weeks.

- Tralokinumab, is a fully human IgG4 mAb that specifically binds to IL-13, a type 2 cytokine, and inhibits its interaction with the receptor. Tralokinumab neutralizes the

biological activity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor. This inhibition decreases the mediators of type 2 inflammation. The recommended dose of this subcutaneous injection is 150 mg every 2 weeks.

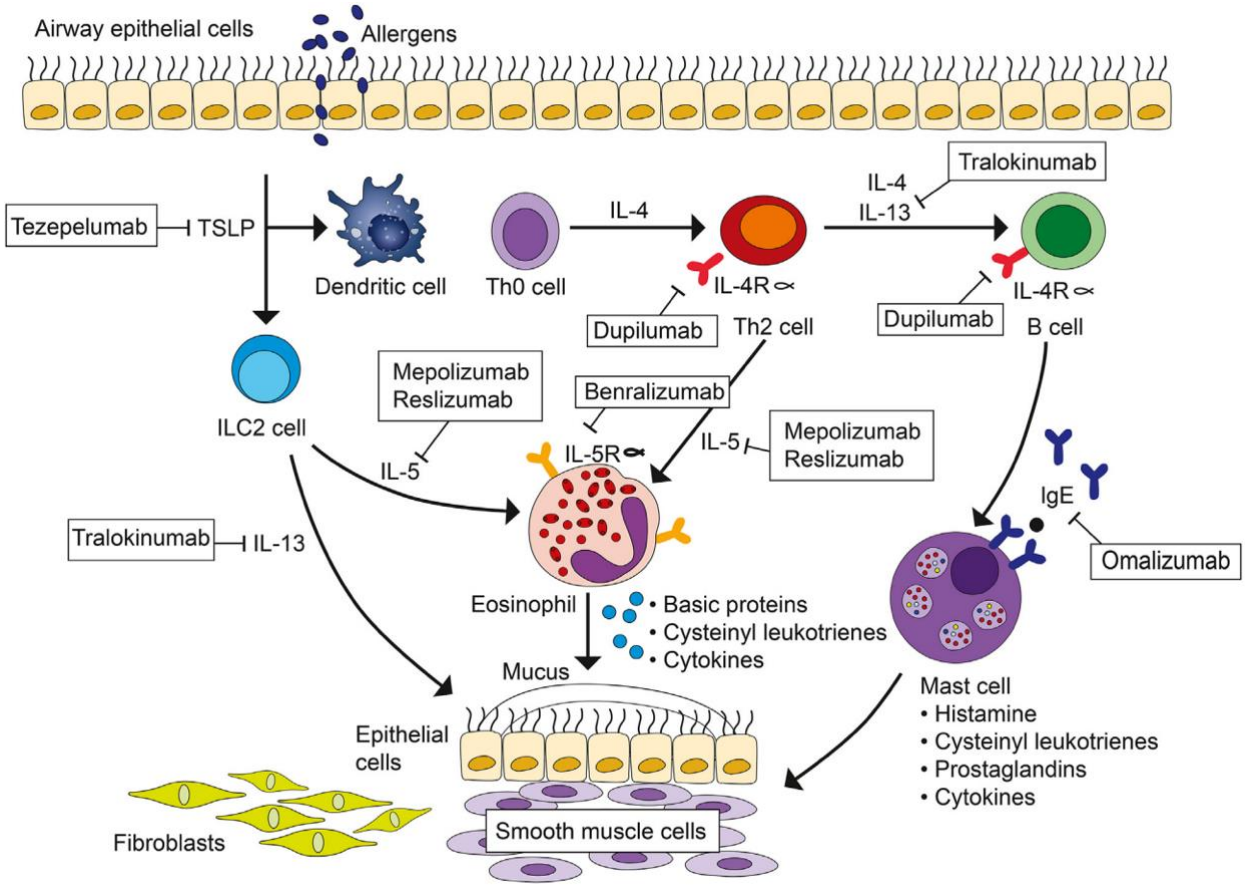

Figure 14. Overview of main mechanism of the currently available biologic drugs FDA-approved for the use in Allergic diseases (30).

Table 6, is a comparison of these biologicals. It contains information on the technical sheet of AEMPS-CIMA and the characteristics of the product, as well as its marketing price in Spain, obtained from BOTPLUS web.

Active substance	Commercial name	Indications	Way of administration	Dosage	Age	Price
Mepolizumab	Nucala®	-Severe eosinophilic asthma. -Chronic rhinosinusitis with nasal polyps. -Eosinophilic granulomatosis with polyangiitis.	Subcutaneously	100 mg every 4 weeks	>6	**1187,59€**

		-Hypereosinophilic syndrome.				
Reslizumab	Cinqair®	-Severe eosinophilic asthma.	Intravenously	3 mg/kg every 4 weeks	>18	**622,87€**
Dupilumab	Dupixent®	-Atopic dermatitis -Severe eosinophilic asthma - Chronic rhinosinusitis with nasal polyps. - Prurigo nodular -Eosinophilic esophagitis	Subcutaneously	200 or 300 mg every 2 weeks	>12	**1318,15€**
Benralizumab	Fasenra®	-Severe eosinophilic asthma	Subcutaneously	30 mg every 4 weeks	>12	**2317,03€**
Tezepelumab	Tezspire®	-Severe asthma	Subcutaneously	210 mg every 4 weeks	>12	**$3633**
Tralokinumab	Adtralza® Adbry® (U.S)	-Atopic dermatitis	Subcutaneously	150 mg every 2 weeks	>12	**1318,15€**

Table 6. Comparison of the biologics for allergic diseases.

Currently, there are other anti-immunoglobulin E (anti-IgE) mAbs for the treatment of allergic diseases. Ligelizumab and Quilizumab are next generation anti-IgE mAbs.

- Ligelizumab is an IgG1κ high-affinity humanized monoclonal anti-IgE antibody. It binds with higher affinity to the Cε3 domain of IgE than Omalizumab. This mAb of Novartis works by blocking the IgE/FcεRI pathway, a key driver of the inflammatory process in CIU. As Figure X shows.

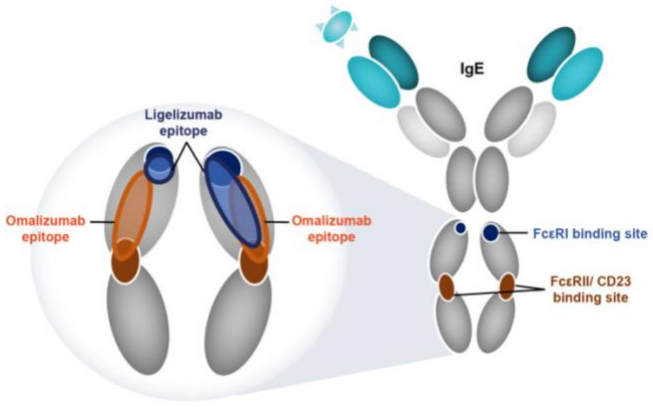

Figure 15. Binding sites of ligelizumab and omalizumab on IgE (31).

In Figure 16, the ligelizumab epitope overlaps with the binding site of FcεRI receptor and has only a minor overlap with the CD23 receptor. The epitope of omalizumab is located more closely to the binding site of CD23. So, ligelizumab inhibits more potently IgE binding to FcεRI than omalizumab, whereas omalizumab blocks IgE binding to CD23 more potently than ligelizumab (31).

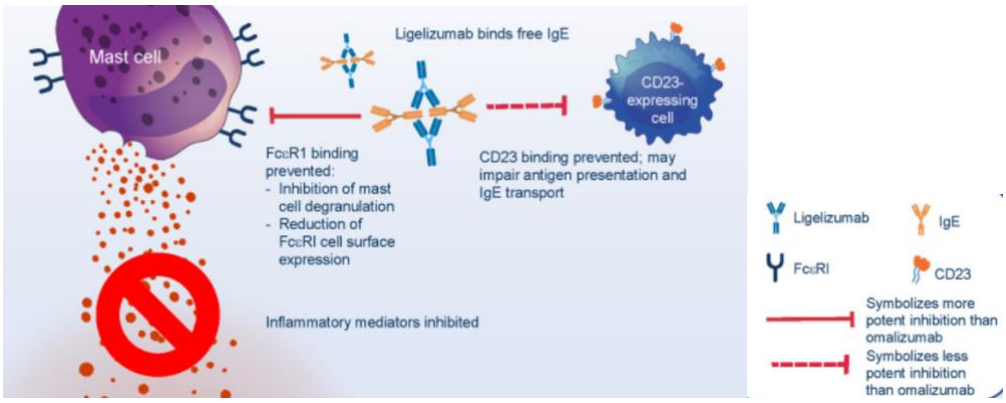

Figure 16. Consequences of ligelizumab-mediated IgE binding blockade to FcεRI and CD23 expressing cells (31).

- Quilizumab, a humanized IgG1 mAb that targets the M1- prime segment of membrane-expressed IgE, leading to depletion of IgE-switched B cells and plasmablasts, it reduces serum IgE levels. This mAb is currently under study.

With the different options and products on the market to treat allergic diseases. How can omalizumab remain a leading medicine for the treatment of severe asthma and chronic urticaria?

The introduction of biologic medicines to the clinical practice increment the demand and use of biomarkers for patient selection, prediction of outcomes and monitoring, to allow the physicians for an appropriate choose of these mAbs (32). Biomarkers are an assessable indicator of the presence and severity of diseases, associating an underlying pathway to a phenotype of a disease. They are important in clinical practice because they bring an objective and measurable strategy to characterize a disease (32). Biomarkers are applied in disease diagnosis, selection of targeted therapy, monitoring and prediction of prognosis. In allergic individuals, these biomarkers are measurable in blood, nasal secretions or sputum (32).

Biomarkers in asthma

Asthma presents four clinical phenotypes; the early-appearance allergic asthma, the early-onset allergic moderate-to-severe asthma, the late-onset nonallergic eosinophilic asthma and the late-onset nonallergic non-eosinophilic asthma (32). To promote an appropriate therapy strategy, asthma can be segmented into Type 2 (high) and non-Type 2 (or Type 2 low) endotypes depended on their underlying inflammatory pathways (32).

Based on these biomarkers with the combination of some physiological parameters, there are guidelines which help to predict a response to targeted treatments and they are also applied to monitor the following treatment response (32). Figure 17 shows the endotypes of asthma with the biomarkers associated and the targeted therapy.

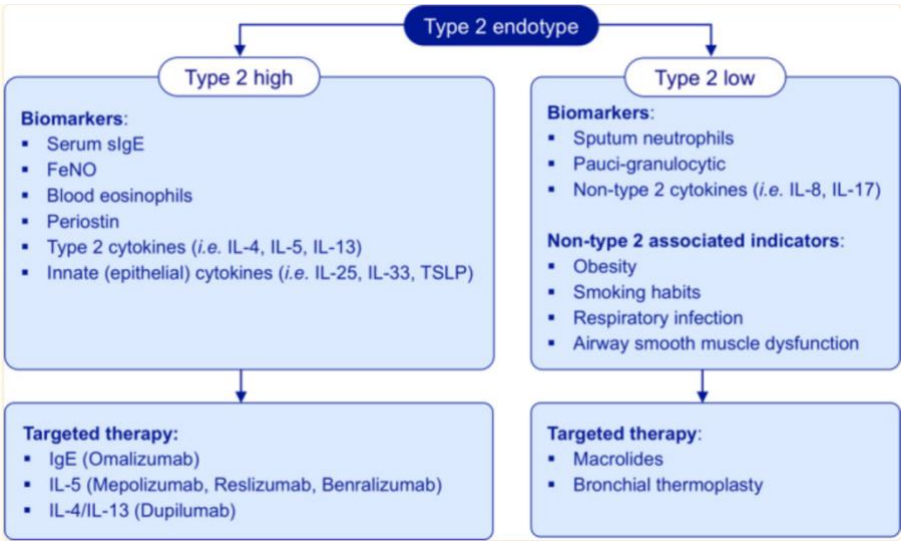

Figure 17. Treatment based on molecular biomarkers for endotypes in asthma (32).

Therefore, phenotyping the patient appropriately is of great importance in clinic, so that he receives the most adequate treatment. That is why, as these mAb have different targets, it has made possible a more personalized treatment for the patient.

DISCUSSION

Omalizumab, the innovative biological that has revolutionized the treatment of allergic diseases, particularly asthma and chronic urticaria, through its specific mechanism of action that targets IgE, a key immunoglobulin implicated in Allergic diseases.
Allergic asthma is a prevalent disease with a complex physiopathology. It represents a clinical challenge and a significant health burden. Furthermore, it is associated with greater healthcare costs and an important impact on a patient´s quality of life.
Traditional treatments often involve the use of inhaled or oral steroids and other medications with potential side effects and less efficacy. There was an unmet need that Novartis identified and covered with this monoclonal antibody (active substance), marketed by the brand name Xolair®, since the consumer needed a revolutionary medicine that did not focus on palliating the symptoms of the disease.

Omalizumab, supposed a revolution, by redefining the paradigm of asthma treatment. It opened up a new alternative world of possible treatments, because it offers a new and alternative treatment option for patients who do not respond well to traditional medicines.
Innovation in health and Pharma is fundamental as it produces value by the creation and application of new technologies, processes, products and services that improve the prevention, diagnosis, treatment and management of diseases and health. Innovation aims to improve people's quality of life by generating new and effective solutions.
The disruptive innovation that Omalizumab supposed was one of the fundamental mechanisms by which the quality of patient´s lives had improved and increased. It represents the change of paradigm from the traditional pharmacological treatments (the small molecules) to these innovative biological drugs more effective and safer.
Innovation is fundamental and inevitable in the pharmaceutical industry. It allows the development of new therapies and treatments that improve people´s health. There are always new demands, as emerging diseases appear, unmet medical needs and competitors, which require new market strategies and business models. The pharmaceutical industry is a highly competitive field so, for a company´s survival and success, breakthroughs are crucial. Disruptive innovation is a strategic pillar in Pharma industry, although it is a costly and risky process that requires significant investment in R&D. However, the success of new drugs can provide significant health benefits for patients.

Omalizumab was a blockbuster drug, a biologic that generated sales of $1 billion. That is because it offered a substantial improvement over the existing treatments for asthma and hives, less effective and with potentially side effects. This successful blockbuster generated significant profits to Novartis and Genentech. Omalizumab is considered a "blue ocean" product on the market because it created a completely new and uninvestigated area in the allergy medication industry. Previously, to the introduction of omalizumab, treatments focused on treating symptoms, and did not focus on treating the underlying cause of the allergy, the physiopathology of the disease.

Omalizumab, on the other hand, directly targets the underlying mechanism of allergy by targeting IgE. Doing so, it provides a new approach to treating allergy that had not been previously explored.

The efficacy and safety of Xolair® has been demonstrated in numerous clinical trials and real-world studies over these two decades in treating severe allergic asthma (SAA) and chronic idiopathic urticaria (CIU). Patients treated with omalizumab have experienced a significant reduction in the severity of symptoms, as well as in the use of rescue medications and hospitalizations. In addition, omalizumab side effects are mild. After its approval and marketing in 2003, it was observed that by blocking IgE, there were also other allergic diseases that could be treated, that is the life cycle management (LCM) of omalizumab. Later on, the indications for the treatment of rhinosinusitis with nasal polyps was approved, and the off-label ongoing investigation for food allergy.

Omalizumab opened up the way to the world of biologics, however, sales of Xolair® have been challenged by fast-growing competitors that enter this field. Among them, benralizumab, dupilumab, reslizumab, mepolizumab and ligelizumab are other biologic drugs approved and marketed that selectively interfere with specific steps in the immune inflammation cascade, as these mAb have different targets, it has made possible a more personalized treatment for the patient. Biological medicines represent the upcoming future of treatments, as they opened up prospects to be able to better control diseases in a safer, precise and more effective way.

In my opinion, pharmaceutical companies should invest more in R&D of biological medicines because of their therapeutic and commercial potential. Since they represent the future of health and bring us closer to the cure of complex diseases that affect a large number of the population. Omalizumab is a clear example of this. They ought to start by making these treatments more

affordable since its high cost can be an obstacle for many patients and health systems and only a percentage of the population benefits from these revolutionary and live-saving treatments.

ANNEX

The annex summarises the interviews conducted with two expert clinicians. Dr. Juan María Beitia, (Allergology Service; University Hospital of Guadalajara) and Dr. Javier Domínguez (Allergology Service; University Hospital La Paz in Madrid). Both professionals have a consolidated background and experience in the use of biologics (including Omalizumab), for treating allergic patients suffering from severe asthma.

Omalizumab, a disruptive innovation for treating allergic patients. Beyond aerosols

Both experts agreed that Omalizumab, such a disruptive product, when it was launched to the market, was well accepted by the medical community. Omalizumab was the very first biological drug approved, in advance, for the treatment of allergic asthma for severe stages. Xolair, the commercial name of Omalizumab, is a revolutionary product for the scientific and medical community. It was the first contact with the world of biologics, and opened the doors to biological medicines. Dr. Beitia and Dr. Domínguez spoke of Omalizumab as an "umbrella" that blocks all the IgE. The product was considered the beginning, of the world of future treatments, of alternatives to conventional medicines that fell short in the treatment of these pathologies and personalised medicine.

According to these two specialists, when patients with these pathologies reach high stages of the allergic disease, the conventional treatments were systemic corticosteroids; however, they induce severe adverse effects and are not effective enough. The dose has to be increased in most of the patients. These severe patients had frequent exacerbations, and therefore emergency hospital admissions, which implies healthcare costs, as Dr. Beitia commented. In addition, treatments with conventional asthma medications are long-term and difficult to the adherence. Omalizumab was the alternative for these patients with severe asthma so badly needed.

As stated by Dr. Beitia, the group of patients treated with this revolutionary drug is not extremely large, but it consumes a lot of resources within allergology. In general terms, patients, allergic patients, poorly controlled are frequently derived to pneumology. They were continuously bouncing between emergency (admissions), pneumology and allergology. They were patients with a very poor quality of life. Omalizumab opened up prospects for the future, to be able to better control asthma in a safer and more effective way.

Regarding safety, mild adverse reactions that patients have experienced during the first few doses of treatment include headache, muscle pain or arthralgia, abdominal pain and in very rare cases, anaphylaxis. Dr. Dominguez said he has had only one case of anaphylaxis in the seventeen years he has been administering this treatment. Patients have a good tolerance to Omalizumab, according to the experts. These adverse effects resolve as they receive more doses.
As a consequence of its subcutaneously administration, it is easy to administer by the patient. The hospital instructs them to, without having to travel to the day hospital. However, as Dr. Beitia commented, these patients require deep monitoring and control.

Omalizumab, under the commercial name, Xolair (Novartis) was the first biologic approved in the European Union for self-administration, and also for pregnant, breastfeeding women, and children, however during the first doses, patients need to be monitored for about an hour. Over the years, doctors confirmed that Omalizumab is a safe drug with mild adverse reactions so patients can self-administer this treatment at home.

Life cycle management of Omalizumab. The progress in the treatment of other pathologies.

The RWE studies, conducted in the last 15 years after the launch of the product, have been confirming the effect of omalizumab in real life. These clinical observations have favoured the life cycle management of the product for new applications.

Concerning the life cycle management of omalizumab, initially, the indication was for severe allergic asthma in severe stages. However, it was found to be more effective in patients in lower stages of severe asthma. Moreover, it was observed that by blocking IgE, there are several allergic pathologies that can also be treated with this biological. It is effective, in a high percentage, in the treatment of chronic spontaneous urticaria, and in the treatment of

rhinosinusitis with severe nasal polyposis after two surgeries. More studies are needed to confirm and demonstrate the efficacy in urticaria, as Dr. Beitia suggested.
Other new biologics, recently launched to the market as Dupilumab, Benralizumab, Reslizumab and Mepolizumab, are being investigated for other applications, but more expensive than Omalizumab. In this case, the mechanism of action remains poorly understood, according to Dr. Dominguez.

Does Omalizumab continue being a "Blue Ocean product"? Competitors

From a competitive point of view, Omalizumab showed clear benefits over other biologics on the market. The following stands out, these specialists highlighted the large amount of safety and efficacy data that have been provided during the seventeen years that this drug has been marketed, besides the well-defined mechanism of how it works. Omalizumab is the best-positioned biologic drug on the market for the treatment of allergic diseases, according to Dr. Dominguez. Other new biologics, recently launched to the market as Dupilumab, Benralizumab, Reslizumab and Mepolizumab, are being investigated for other applications, but they are more expensive than Omalizumab. In this case, the mechanism of action remains poorly understood, according to Dr. Dominguez.

For the correct use of these new biologic drugs, it is necessary to phenotype the patient and to investigate if asthma is caused by IgE, eosinophils, interleukins, etc. According to these results, other biologics could be more effective than Omalizumab. This is a clear example of innovation based on previous studies and products. Companies developing biologics for treating similar diseases used the knowledge generated by disruptive innovation. One of the most controversial issues regarding biologics is that not all patients can be treated. The use of biologics requires expert committees in hospitals that select patients. These committees are composed by medical management, pharmacy, pneumology, psychiatry, otolaryngology and allergology.

What about incremental innovation?

One of the topics non solved until now is the long-term efficacy of Omalizumab. Biologics consists of chronic treatments, because they do not modify the course of the disease. For allergy treatment, only specific allergen immunotherapy modifies the course.

Doctors were asked about the effectiveness in the combination of immunotherapy with Omalizumab for treating different allergies. Omalizumab is being used for reducing the levels of IgE in milk and egg desensitisation because it increases the tolerance threshold in oral immunotherapy. The tricky thing is that it transiently blocks IgE, so that many patients react again on withdrawal. These treatments, as Dr. Domínguez commented, are off-label. These studies suggest a clear opportunity for developing incremental innovation of the product, or even to revise the life cycle management. These studies suggest a clear opportunity for developing new formulas.
Nevertheless, to provide a patient with these treatments, due to the high cost of the drug, it is not viable at the moment, as you would have to provide Omalizumab for life.

To sum up, Omalizumab targets the pathophysiological basis of asthma, by blocking IgE. The consequence is blocking the reaction and induce the inflammation resulting from the activation of that protein to be reduced. Omalizumab has a holistic effect. Dr. Beitia believes that biologics are the future, they open up a world that we did not have until recently, but we have to be consistent with the situation, Spain cannot afford it, the health system would go bankrupt, so we have to control which patients receive the drug. Dr. Domínguez told me the same thing, that these drugs improve the quality of life of the patient. It is a very safe and effective drug, but still very expensive.

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