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ZINBRYTA'S LEGACY: UNRAVELING THE DUAL EDGES OF CD25-TARGETED THERAPY IN MULTIPLE SCLEROSIS

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ABSTRACT

Background: Multiple sclerosis (MS) is a persistent neurodegenerative autoimmune disease, which is demyelinated through immunological means. Interleukin-2 (IL-2) signalling is a therapeutic target because it is involved in the progression of the disease. Zinbryta (daclizumab) was designed to regulate the immune response in patients with relapsing multiple sclerosis.

Methods: The efficacy, mechanism of action and safety profile of daclizumab have been evaluated using evidence presented by pivotal clinical trials (SELECT, DECIDE), long-term extension studies (SELECTED) and post-marketing surveillance.

Results: Daclizumab resulted in a significant decrease in annualized relapses and magnetic resonance imaging-detectable disease activity, accompanied by an increase in CD56bright natural killer cell pools, which are associated with immune regulation. Prolonged research proved the long-term disease control and disability progression stabilization. Nevertheless, serious adverse events such as hepatotoxicity, cutaneous reactions, infections and immune-mediated encephalitis were frequent.

Conclusion: Although it has been demonstrated to be clinically effective, unacceptable side effects prompted a worldwide recall of daclizumab in 2018. The case identifies the significance of long-term safety observation and immunomodulation as an essential part of MS drug development.

KEYWORDS

Zinbryta legacy, Multiple sclerosis and Immune regulation.

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INTRODUCTION

Background Information

Multiple sclerosis (MS) develops as an autoimmune neurodegenerative condition due to immune-mediated damage of myelin. Genetic expressions through HLA-DRB1 combined with environmental factors such as infections and vitamin D deficiency and smoking behavior alter the inflammatory response and neurodegenerative patterns while affecting disease progression.

Vitamin D deficiency appears to be linked with lower sunlight exposure areas because women experience higher MS prevalence (3:1 ratio) among 2.8 million global MS patients. People develop this condition between 20 to 50 years old close to the equator where it is more common (Mubarak Alruwaili *et al*, 2023)¹.

DRUG AND MECHANISM OF ACTION

Zinbryta (Daclizumab) functioned as a monoclonal antibody to treat relapsing MS by targeting IL-2 receptor (CD25) and controlling immune responses through T-cell suppression and CD56bright NK cell enhancement. The pharmaceutical industry discontinued Zinbryta in 2018 because it caused substantial liver inflammation and adverse immune responses (“Learn about Expert Review of Clinical Pharmacology,” 2018)².

DRUG DISCOVERY

Research on Zenapax began in 1997 as an anti-transplant rejection medicine that targeted IL-2 receptor (CD25).

Clinical studies SELECT and DECIDE demonstrated that Zinbryta reduced MS relapses through immune system mediation.

FDA granted Zinbryta approval in 2016 to treat relapsing multiple sclerosis by allowing patients to receive one monthly injection which decreased disease activity and relapse rates.

The pharmaceutical company withdrew Zinbryta voluntarily from markets because the drug presented serious safety risks that resulted in liver damage along with immune system complications and brain inflammation (Forsthuber *et al*, 2020)³.

CLINICAL TRIAL

In Phase 2 (SELECT Trial) patients exhibited decreased MS relapse frequencies coupled with enhanced MRI-detectable disease activity while their CD56bright NK cell numbers for immune regulation grew.

During Phase 3 (DECIDE Trial) mipasartan outperformed IFN- β through its ability to reduce relapses and MRI lesions at the cost of severe side effects including liver dysfunction.

Safety review became necessary after EMA received reports about serious inflammatory brain

conditions along with severe liver damage which resulted in cases of encephalitis and meningoencephalitis (Forsthuber *et al*, 2020)³.

PUBLIC PRIVATE PARTNERSHIP

Zinbryta (Daclizumab) is a joint development from Biogen and AbbVie. It focuses on neurology and immunology to manage relapsing multiple sclerosis (MS).

Zinbryta gained FDA approval in May 2016 and subsequent EMA approval in July 2016. In March 2018, Biogen and AbbVie permanently discontinued Zinbryta worldwide because of dangerous inflammatory brain diseases and increasing doubts about its safety-to-benefit ratio.

REAL LIFE CASES

Four hundred and ten participants received Daclizumab beta (150mg every 4 weeks) as treatment in 66 centers across eight countries through the SELECTED study that lasted up to six years.

The initial annualized relapse rate (ARR) was 0.21 with low annual relapse rate maintenance alongside decreased disability progression in 17.4% of patients while MRI imaging showed decreased new lesion formation and brain tissue preservation improved over time.

Safety Concerns involved 87% of patients who reported adverse events with 26% having serious AEs and 25% presenting liver toxicity and 38% having skin-related reactions and 61% developing infections.

The drugs Zinbryta experienced withdrawal from the entire global market following reports of major liver toxicity and immune-related health complications during March 2018 (Gold *et al*, 2020)⁴.

SAFETY AND EFFICACY

The clinical benefits of Zinbryta included its effectiveness in controlling MS disease activity and low ARR rates with disability maintenance and brain volume protection.

Liver-related adverse events occurred in 16% of patients while liver enzyme elevations affected 10% of patients until some required stopping treatment.

Cutaneous reactions related to rash and eczema occurred in 33% of patients yet 59% received treatment for infections among which 2% developed opportunistic infections.

Safety concerns beyond MS included gastrointestinal problems (Present in 25%) as well as serious events (16%) such as immune-based complications and additional non-MS related adverse events reported from treatment with Zinbryta.

The FDA compelled Biogen and AbbVie to remove Zinbryta worldwide in March 2018 due to significant liver damage and immune dysfunction although the drug proved effective for patients (Gold *et al*, 2020)⁴.

LIMITATIONS

A considerable proportion (42%) of participants withdrew from the study, while 45% discontinued the treatment because of adverse events (AEs) and consent withdrawal or investigator decisions that reduced the validity of extended-term data collection.

The study design, an open-label single-arm trial, omitted placebo and active treatment groups, which prevented direct comparison between MS therapeutic options for efficacy and safety measures.

The selection bias occurred when individuals who tolerated the drug well chose to stay in the study. As such, screening excluded patients who faced severe adverse early effects.

After year 4 of the study, a reduction in MRI scans prevented long-term analysis of MS disease activity and brain volume measurement (Gold *et al*, 2020)⁴.

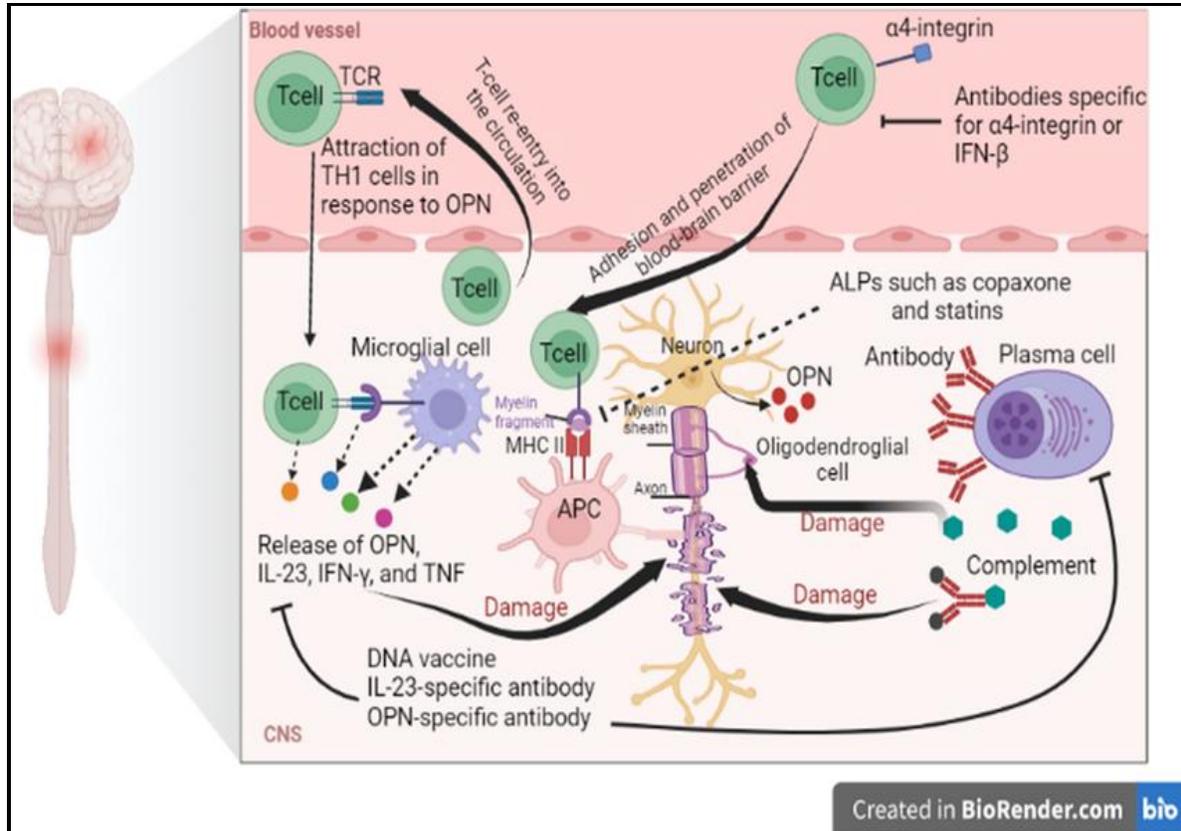


Figure No.1: Pathophysiology of multiple sclerosis (Mubarak Alruwaili *et al*, 2023)¹

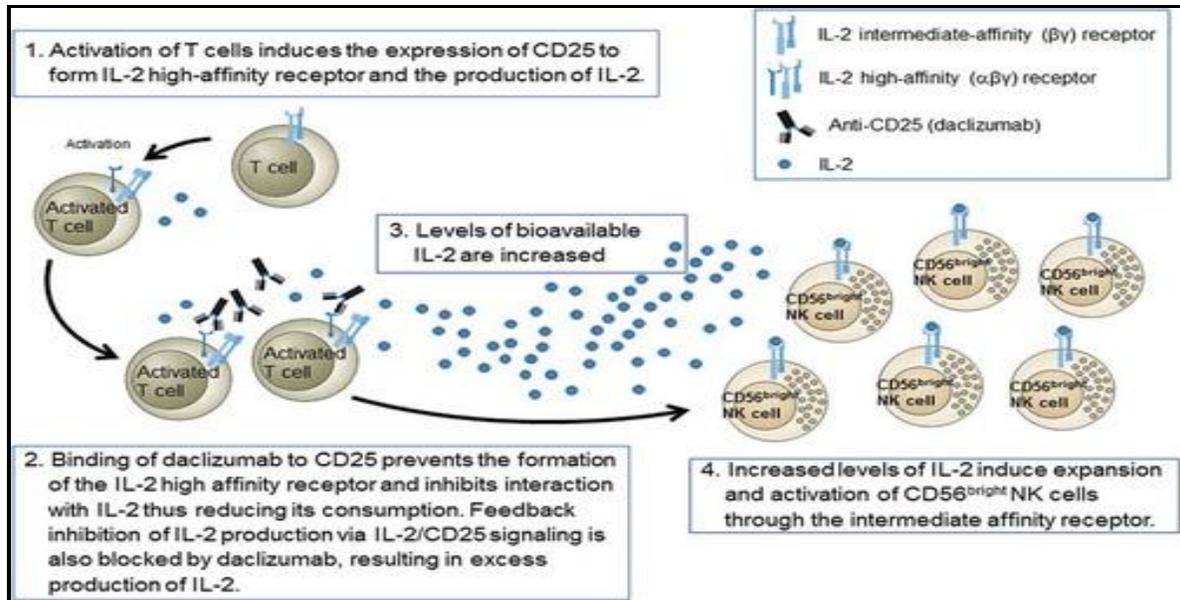


Figure No.2: Mechanism of Action of Zinbryta (Daclizumab) (“Learn about Expert Review of Clinical Pharmacology,” 2018)²

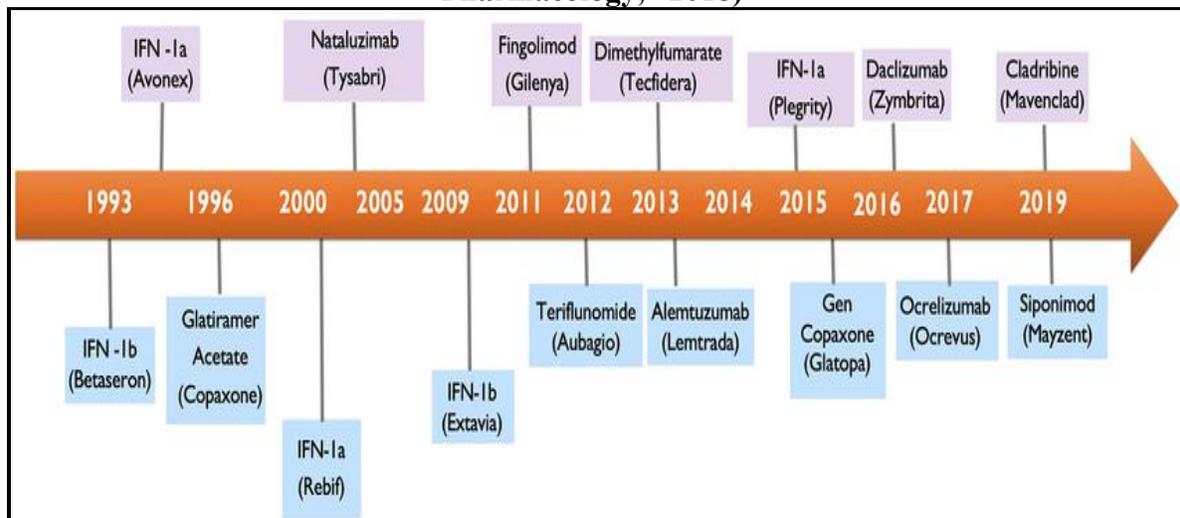


Figure No.3: Timeline for Drug Discovery process of Zinbryta (Daclizumab) (Forsthuber *et al*, 2020)³

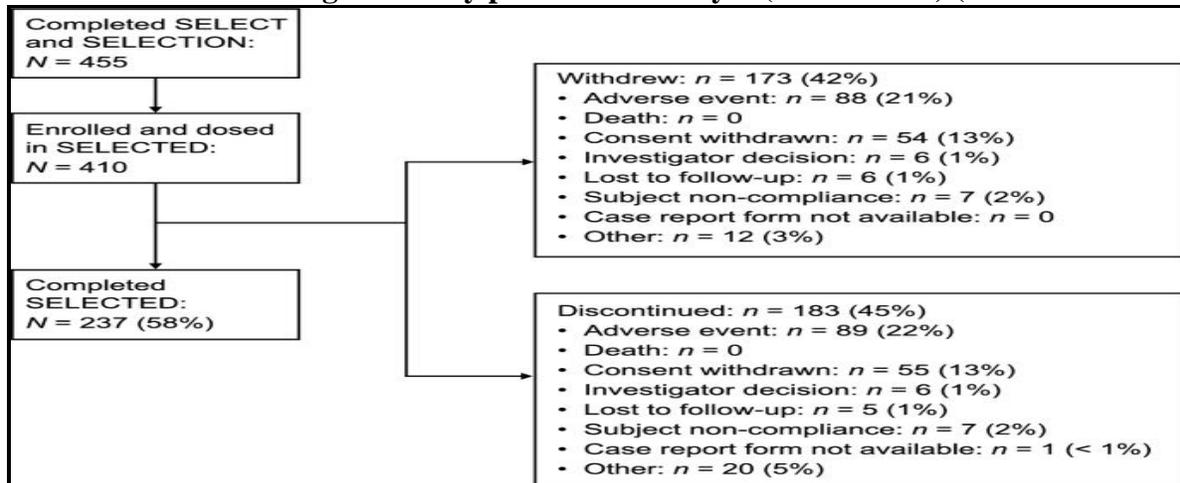


Figure No.4: Flowchart of data analysis of AEs and SAEs of Zinbryta (Gold *et al*, 2020)⁴

PUBLIC PRIVATE PARTNERSHIP



FUTURE IMPLICATIONS

The development of new MS treatments must direct immune pathway interventions toward medications that exhibit minimal systemic toxicity while achieving both safety benefits and effective therapeutic outcomes.

The future research agenda should investigate different CD25-modulating therapies combined with new monoclonal antibodies to attain Zinbryta-like therapeutic results while reducing immune complications.

Drug development strategies require longer pre-market testing followed by better early safety checks that should occur prior to obtaining regulatory approvals (Gold *et al*, 2020)⁴.

CONCLUSION

The long-term effectiveness of Zinbryta for lower MS relapse rates and disease progression worked against its detrimental side effects that included hepatic toxicity and infections with additional immunological complications.

The treatment effect of Zinbryta lasted over extended periods due to its ability to decrease MS disease activity while maintaining stable disability progression and preserving brain volume for up to 8 years.

A high percentage (87%) of serious adverse effects with severe liver damage (25%) and infections (61%) and skin reactions (38%) resulted in Zinbryta treatment stoppages at a rate of 45% .

In March 2018, Biogen and AbbVie decided to withdraw Zinbryta from all markets because of severe immune-mediated risks that caused encephalitis and hepatic complications so the European Medicines Agency suspended its marketing authorization (Gold *et al*, 2020).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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