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Asparaginase Erwinia: An Effective Bacteria-Derived Enzymes in Acute Lymphoblastic Leukaemia Chemotherapy

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ABSTRACT

L-asparaginase is an antitumor drug that is utilised in the treatment of acute lymphoblastic leukaemia. For nearly three decades, it has been an essential component of paediatric acute lymphoblastic leukaemia treatment procedures. In this review, we explain the acute lymphoblastic cancer and relation between Asparaginase (ASN) and Acute Lymphoblastic cancer (ALL). A careful evaluation of the possible pharmacologic and experimental of several provisions of L-asparaginase as a medication has been attempted. The benefits of PEG-l-asparaginase over instinctive preparations, as well as the history of L-asparaginase therapy, are discussed in the following review.

Keywords: Acute Lymphoblastic Leukemia; Asparaginase; Pharmacokinetics; Pharmacodynamics; Extranodal NK/T Cell Lymphom

Abbreviations: ALL: Acute Lymphoblastic Leukemia; ASN: Asparaginase; CD47: cluster of differentiation 47 ; CTC: Common Toxicity Criteria; CXCR4: C-X-C chemokine receptor type 4; CXCL12: C-X-C chemokine ligand 12; CSF: cerebrospinal fluid; ENKTL: Extranodal NK/T Cell Lymphoma; G-MDSC: Granulocytic Monocyte Derived Suppressor Cells; MSCs: vascular niche; NK: natural killer; PD: Pharmacodynamics; PEG: polyethylene glycol; PK: Pharmacokinetics; Reactive oxygen species (ROS); Regulatory T cells (Tregs); SIRP: Signal regulatory protein; TGF-β: immunosuppressive transforming growth factor; MSCs: Mesenchymal stem cells

Introduction

Acute lymphoblastic leukaemia (ALL) is a malignancy of lymphoid are cells that divided into immunophenotypic groups: precursor B cell lymphoblastic leukaemia, T cell ALL and mature B cell ALL. ALL has an etiology that is still unknown [1]. While some risk factors have been found, such as excessive ionising radiation exposure and genetic disorders like ataxia-telangiectasia, Down syndrome, and Bloom syndrome etc [2]. ALL is mainly found cancer in children, with 50% of all cases diagnosed each year in the United States occurring in children and under the age of 20. Through various interactions, the leukemic microenvironment promotes the survival of ALL cells and their immune evasion [3]. The microenvironment of leukemia is shaped by a variety of cell types. Regulatory T cells (Tregs) release inhibitory cytokines that limit macrophage phagocytosis and lower T cell cytotoxicity. T lymphocytes and reactive oxygen species (ROS) inhibit natural killer (NK) cells produced by Granulocytic Monocyte Derived Suppressor Cells (G-MDSC).

The control of histocompatibility group of class-1 related chains is reduced in ALL cells in A/B (MIC-A/B), although NK cells have lower amounts of natural cytotoxicity triggering receptor p46

(NKp46) activating receptor. ALL affects NK cell dysfunction by releasing (TGF-β) immunosuppressive transforming growth factor. C-X-C chemokine ligand 12 (CXCL12) is released by mesenchymal stem cells (MSCs) and interacts with C-X-C chemokine receptor type 4 (CXCR4), allowing ALL to engraft into the vascular niche. MSCs also defend ALL cells from galectin-3 secretion treatment, which stimulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-β) pathway, which activates the nuclear factor kappa-light-chain-enhancer of activated MSCs also secrete chemicals that reduce L-cytotoxicity. Non-classical (CD16+) monocytes from asparaginase are thought to play a role in ALL cell protection and enter the leukemic milieu. The leukemic niche's macrophages develop immunosuppressive characteristics and produce the tumor-promoting cytokine TGF- β. Signal regulatory protein (SIRP) interacts with cluster of differentiation 47 (CD47), a «don't eat me signal» conveyed by leukemic cells, lowering phagocytic activity [4-8] Figure 1.

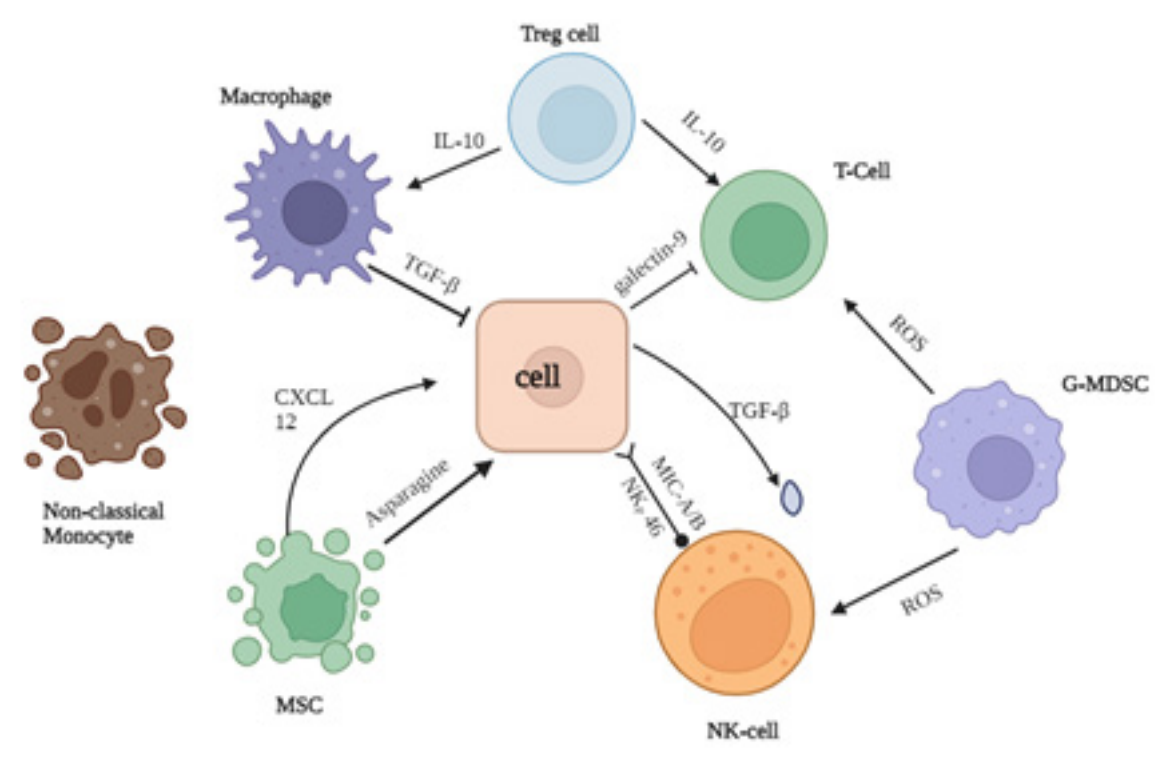

Figure 1: Representation of links of multiple pathways with ALL.

Asparaginases, which are bacteria-derived enzymes, are one of the medications used to treat ALL. So far, three different kinds of asparaginase have been used:

a. Escherichia coli-derived native asparaginase (E. coli asparaginase: Kidrolase, EUSA Pharma, Oxford, UK; Elspar, Ovation Pharmaceuticals, Deerfield, Illinois; Crasnitin, Bayer AG, Leverkusen, Germany; Leunase, Sanofi-Aventis, Paris, France; Asparaginase Medac, Kyowa Hakko, Tokyo, Japan),

b. Asparaginase from E. coli that has been pegylated (polyethylene glycol [PEG]-asparaginase: Oncaspar, Sigma-Tau Pharmaceuticals, Inc., Gaithersburg, MD),

c. Erwinia asparaginase is an enzyme isolated from Erwinia chrysanthemi (Erwinase, EUSA Pharma, Oxford, UK). [9-11]

It's worth noting that not every country has access to all of these precautions. A fourth proprietary of recombinant E. coli asparaginase preparation is now in clinical testing; it is designed to have an amino acid arrangement equal to Asparaginase Medac, initial studies show effectiveness and toxicity profiles similar to prior E. coli-asparaginases [12]. asparaginase contained in homologous RBC has been presented as a novel technique for preserving enzyme function while decreasing the development of anti-asparaginase antibodies. In a preclinical context, a pegylated arrangement of recombinant Erwinia asparaginase has also been explored. Asparaginase induces quick and complete deamination of the amino acid asparagine and, to a lesser extent, glutamine,

resulting in asparagine depletion, mainly in plasma and, to a lesser extent, cerebral fluid [13]. It's been claimed that different E. coli asparaginase preparations have different biological activities. The acceptable dose has changed between trials, showing that the relative strength of the asparaginase products on the market varies. Despite its usage as a critical medicine for ALL, the proper formulation and dosage of asparaginase are still debated [14].

Anti-Cancer Potential of Asparaginase

To maintain with their uncontrollable malignancy, tumour cells, notably lymphatic cells, require a large amount of asparagine. This means they satisfy their huge L-asparagine need with both asparagine from the diet (blood serum) and generated themselves [15]. As a medication, L-asparaginase takes advantage of tumour cells' exceptionally high need for the asparagine. L-asparaginase is a kind of enzyme that act as catalysis in the conversion of L-asparagine to L-aspartic acid (Figure 2) [16]. Because ALL cells are deficient or have very low levels of L-asparagine synthase, they cannot manufacture L-asparagine from scratch and must depends on asparagine from the bloodstream to survive and proliferate. L-asparaginase causes a decrease in level of asparagine in serum, which terminates tumour cells by neglecting them of a necessary component for protein synthesis [17]. Healthy cells, on the other hand, are unharmed since they can produce asparagine through the enzyme L-asparagine synthase, which is abundant. Cell death was assessed in patients with ALL who were administered l-asparaginase as a single medication, according to Asselin, et al. [18]. Apoptosis was caused by cell cycle arrest in the G1 phase in the murine L5178Y cell line as well as the MOLT-4 mediated by T-lymphoblastoid line. Asparaginase inhibits an anthropological ALL cell line, with Erwinia caratovora L-asparaginase having a 10-fold greater effect [19-22].

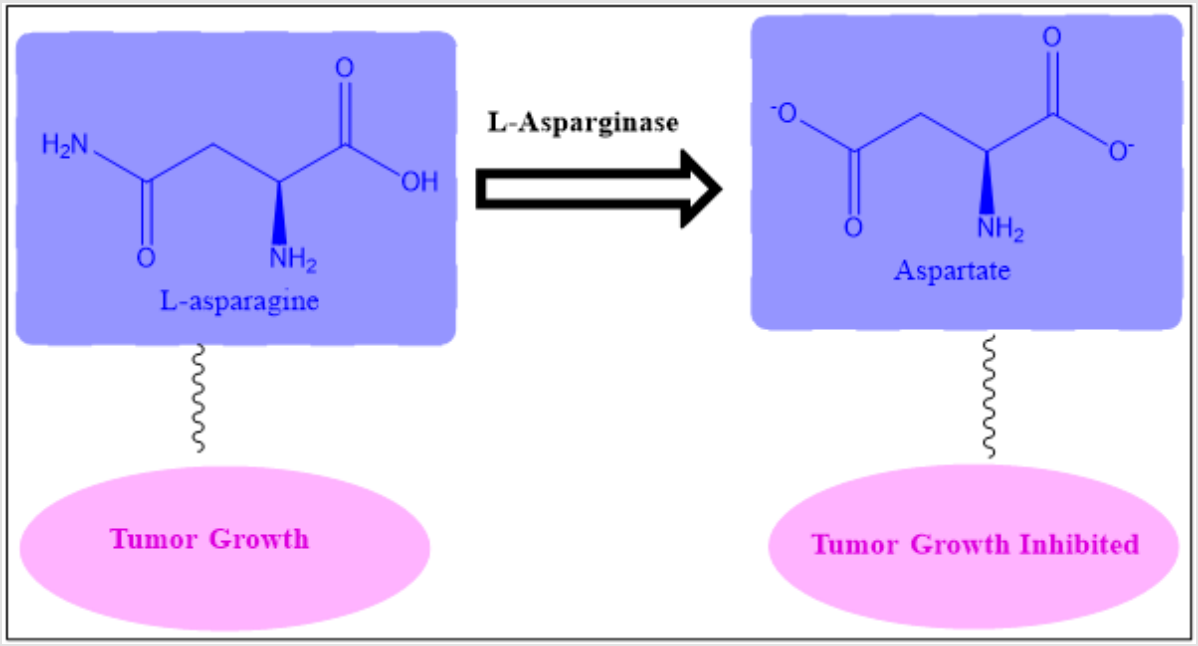

Figure 2: Schematic representation of mode of action of L-asparaginase.

Chemical and Pharmacological Aspects of Asparaginase

Using different E. coli strains, distinct L-asparaginase have been identified. Recombinant E. coli L-asparaginase has a molecular weight of 133–141 kDa. All asparaginases are made up of four subunits, each of which has an active site and has a molecular weight of 22 kDa [23]. According to Korholz et al. the molecular weight of each component in E. coli L-asparaginase is roughly 32 kDa, but it is 40 kDa in Erwinia preparations. The molecular weight of Erwinia L-asparaginase has been found to be 138 kDa [24]. The enhanced enzyme has a different potential of 300-400 mol/min per milligrams of protein for E. coli, the isoelectric point is between pH 4.6 and 5.5, whereas for Erwinia, it is approximately pH 8.7 [25]. L-asparaginase has a Km of approximately 1105 mol/l. Because all attempts to abolish this glutaminase activity have failed, and uniform recombinant L-asparaginase has L-glutaminase activity, it appears that L-glutamine hydrolysis is mediated by L-asparaginase. [26].

Table 1: Glutaminase activity in different L-asparaginases (%).

Source	Glutaminase activity (%)	Specific action
Guinea pig serum	0	50
E. coli	2	270
Serratia	5	60
Erwinia	10	700

Table 2.

	E. coli		Erwinia (native)
	Native	PEGylated	
Activity (IU/mg protein)	280-400	280-400	650-700
Km (µM)-L-asparaginase	12	12	12
L-Glu/L-Asp (maximal activity)	0.03	0.03	0.1
Km (µM)-L-glutaminase	3000	3000	1400
PI	5	5	8.7
Molecular weight	141000	-	138000

Despite the lack of glutaminase activity in guinea pig L-asparaginase (Table 1), It has not been accessible in sufficient quantities for clinical research [27]. The purity and properties of Erwinia and E. coli enzymes have been intensively investigated, and Table 2. lists some native and modified preparations [28]. High immunogenicity to the foreign protein, with responses ranging from mild allergy to anaphylactic shock in around 25% of patients, and a relatively short half-life value limit the use of native L-asparaginase for further treatment [29]. To prevent the need for frequent intramuscular injections, efforts have been made to reduce the drug's immunogenicity while maintaining its action and increasing its half-life. Chemical alteration appears to satisfy these needs to some extent. In the late 1970's, a number of organisations commenced chemically adjusting L-asparaginase in various ways in an attempt to create a form that was less immunogenic while yet having good anticancer movement [30].

This was only conceivable using techniques that could conceal immunogenically active epitopes without jeopardising the drug's anticancer properties. PEGylation, which involves conjugating L-asparaginase to PEG, was the most successful chemical alteration [31]. In the 1970s and 1980s, it was created. PEG and L-asparaginase were successfully coupled for the first time by Abuchowski, et al. The tumor-bearing BDF mouse model L5178Y was used to assess the antileukemic properties of this novel preparation. The drug's immunogenicity was eliminated once the enzyme was coupled to PEG. PEG L-asparaginase, commonly known as pegaspargase, has biochemical properties that differ markedly from those of the native enzyme [32]. It has a higher apparent molecular weight. It has a limited reactivity with certain antibodies, although this rises when the medication is frozen and thawed. Clinical trials have shown that the enzyme has anticancer efficacy in both animal and human models. The reduced immunogenicity in vivo was validated in highly sensitised children with several ALL relapses. During the polyethylene glycol-L-asparaginase therapy, Ettinger, et al. reported no allergy, reduced occurrences of hyperglycemia, and pancreatitis.

Pegaspargase is the generic term for commercially available treatment formulations, while ONCASPAR is the emblem of the producer, ENZON, of South Plainfield, NJ [33]. Many more chemical transformations were attempted, each with its own set of disadvantages. The addition of L-asparaginase to dextran was also investigated in order to improve thermal and proteolytic stability as well as immunogenicity, however the lessening in immunogenic toxicity was less effective than with PEG. Uren and Ragin used poly-dl-alanyl peptides to suppress immunogenic epitopes of E. coli and Erwinia L-asparaginase in E. coli and Erwinia L-asparaginase in 1979, but no clinical trials have been conducted since then. Nerker and Gangadharan coupled Erwinia L-asparaginase to human serum albumin in 1989. In this scenario, in vivo experiments are also pending. Acylation has also been used to modify L-asparaginase, although this method has the disadvantage of making the enzyme hydrophobic after modification. The half-life of L-asparaginase entrapped in red blood cells was significantly extended in vivo.

Intravenous infusion of L-asparaginase in mice resulted in efficient clearance of the enzyme for two weeks, although the enzyme's immunogenicity was only marginally reduced. Palmitoyl L-asparaginase, a chemically modified form of the enzyme encased in a liposome, was also tested in animals and showed a 10-fold increase in half-life without causing acute toxicity [34-36].

Pharmacokinetics Activity

The pharmacokinetics of any medicine are significantly influenced by the manner of administration. Furthermore, it was established that it is also dependent on the type of preparation employed as well as the administration manner. The half-lives of L-asparaginases in Erwinia and E. coli are comparable in vivo, according to in vivo research having a mean half-life of 10 hours [37]. L-asparaginase was found to be helpful in the treatment of meningeal leukaemia in one research. According to various studies, those people who become hypersensitive to natural L-asparaginase molecules have a shorter enzyme half-life. The enzyme's early clearance from plasma follows first-order kinetics. The half-lives of the three preparations varied. L-asparaginase from E. coli has a half-life of 14–22 hours. After the injection. The peak activity lasted around 3 hours. Enzyme activity was detected 13–22 days after a single injection [38]. The enzyme accumulated in the bloodstream after daily therapy. Plasma asparagine levels dropped fast after

enzyme delivery, to virtually undetectable levels. After a single dose, asparagine was detectable in plasma 23–33 days later. Erwinia L-asparaginase had a t1/2 of 0.65 0.13 days. Serum activity peaked within 24 hours of administration and was no longer detectable by day 7 [39].

Because asparaginase activity well beyond the therapeutic range may result in increased toxicity, trials with lower asparaginase dosages were done in a small number of people. Reduced induction dosages of 10000 IU/^{m2} to 5000 IU/m^2 and even 2500 IU/m^2 given at 3-day intervals were found to be sufficient to deplete ASN in blood and CSF. The reduction in hypersensitivity reactions was connected to the re-induction of E. coli enzymes and asparaginase erwinia. Supporting the hypothesis that switching medications on a frequent basis could help to reduce immunological reactions [40]. A regular intravenous injection of L-asparaginase generated by E. coli was proven to be beneficial in a study of patients with metastatic cancer and leukemia. The cumulative impact resulted in an increase in plasma levels. Peak plasma levels of asparaginase were measured in individuals with metastatic cancer and leukaemia 14 to 24 hours after intramuscular injection. At its peak, native E. coli asparaginase activity can be detected 24 to 48 hours after injection [41-42].

Pharmacodynamic Activity

Asparaginase medication reduced plasma asparagine levels from an average of 41 μM to less than 3 μM in clinical investigations of patients with previously untreated risk of ALL. In this study, asparaginase therapy reduced cerebral fluid asparagine levels from 2.8 μM (pre-treatment) to 1.0 μM and 0.3 μM on days 7 and 28 after induction, respectively. Asparagine depletion occurs 14 to 23 days after bacterial asparaginase injection. [43]. Many people believe that there is a straight forward connection between asparaginase activity and ASN levels in the blood. Endogenous probably hepatic synthesis with this amino acid, as well as anti-asparaginase antibodies of low or high titers, may influence ASN levels. Because asparaginase is a foreign protein, it becomes immunogenic. The role of IgG4 in allergic responses is well recognized. Patients may have antibodies even if they don't have a clinical allergy. In newly diagnosed individuals, treatment failure was linked to the anti-asparaginase antibodies of high titre are being developed. In further two clinical trials, the frequencies of anti-asparaginase antibody positivity were identical.

An allergy to asparaginase has not been associated to a poor outcome. The large and single application of PEG-asparaginase was claimed to have lowered the prevalence of anti-asparaginase antibodies in half in the Children's Cancer Group (CCG)-1962 research. [44]. ASN depletion is better associated with improved responsiveness, still there was really no correlation between depletion and enzymatic activity. ASN depletion was obviously absent in around one-third of the individuals [45]. Regardless of medication composition, the author discovered a stronger relationship among asparaginase expression and glutamine depletion in blood and cerebrospinal fluid (CSF) during induction in newly diagnosed patients, previously untreated standard-risk ALL patients involved in the CCG-1962 study. Despite substantial asparaginase activity, detectable quantities of ASN were found in the plasma and CSF of a subset of these people [46-47].

Toxicity Study of Asparaginase

Asparaginase has a unique profile that includes hyperglycemia and immediate responsiveness to hepatic damage and pancreatitis are all possibilities. There are two types of asparaginase toxicity: those that produce immunological hypersensitivity to a foreign protein, as well as those that decrease protein production [48-49]. The incidence of toxicity is consistent across all asparaginase preparations which are commercially available in the instance of pegaspargase however, allergen responses are inhibited. In contrast to other chemotherapy medications used in multi-disciplinary therapy regimens, L-asparaginase has minimal effect on bone marrow and typically has no effect on the mucosa of the digestive tract, the oral cavity or hair follicles. An overview of lethal effect and recommends the way to evaluating clinical hypersensitivity using the National Cancer Institute's Common Toxicity Criteria (CTC) as shown in Table-3 [50].

Allergic responses might range in symptoms vary from moderate erythema to systemic anaphylaxis. Indurations, edoema, swelling, cold, fever, discomfort, and skin rashes are some of the other documented hypersensitive responses. It has been reported that fatal anaphylaxis can occur up to 4 hours following injection. Antihistamines can sometimes cure or prevent urticaria. However, other more severe responses frequently need cessation of the specific type of the medication provided. Although there have been reports of desensitization treatments for the sample size for L-asparaginase hypersensitivity was insufficient to yield any statistically significant findings. A significant number of patients must be studied for a prolonged period of time in order to demonstrate the therapeutic significance of this discovery [51].

Table 3: Adverse event with General management compared with Asparaginase.

Adverse Event	General Management	Asparaginase Management
Clinical hypersensitivity	Treat symptoms in accordance with institutional guidelines. May pause infusion for local reactions Immediately stop infusion for systemic reaction.	Switch patient to immunologically distinct asparaginase for grade 2 or greater hypersensitivity.

Hyperbilirubinemia	In adults, it is generally recommended to hold asparaginase in patients with a direct bilirubin slightly higher level than 3 mg/dl.	Switch patient to immunologically distinct asparaginase for grade 2 or greater hypersensitivity.
Hyperglycaemia	Monitor patient blood glucose. Exercise, diabetic dietary modifications Treat as medically indicated	No dosage adjustments are necessary. Continue asparaginase for uncomplicated hyperglycaemia.
Pancreatitis	Bowel rest Provide adequate fluid therapy and pain management. Monitor for pancreatic-enzyme elevation or pseudocyst formation. Imipenem antibiotics and octreotide can be considered.	Pause for acute pancreatitis until symptoms subside and amylase levels return to normal.
Silent inactivation	No overt symptoms; can only be identified with asparaginase activity measurement	Switch to immunologically distinct asparaginase if trough asparaginase activity is less than 0.1IU/ml.
Venous thromboembolic event	Anticoagulation therapy with low-molecular-weight heparin At-risk adults may be treated with antithrombin or fibrinogen replacement therapy with antithrombin III concentrates or cryoprecipitate	Hold asparaginase for clinical thrombosis. Resume asparaginase once symptoms have resolved and recanalization has been confirmed. Discontinue entirely in the event of grade 4 central nervous system thrombosis.

*Note: Based on information from National Cancer Institute.

Fatty acid infiltration of the liver is a frequent pathological finding after L-asparaginase treatment. When a medication is cleared or stopped, hepatic functions typically return to normal. The mechanism of coagulation, as shown by abnormalities in the synthesis of plasma protein, is a typical adverse effect of L-asparaginase treatment. While low clotting factor levels have been repeatedly established, there are two types of asparaginase toxicity: those that cause hypersensitivity to a foreign protein and those that cause protein synthesis suppression [52].

Clinical study of Asparaginase

Various combinations have been tried to overcome the toxic effects of Asparaginase and the combinations followed for the trials are discussed below. Given the hypersensitivity associated with the medication's original formulations of drugs that have been changed appear for gaining the prominence in therapeutic applications [53].The PEGylated enzymatic activity is recommended over any of the currently accessible native formulations, which have now been shown to be safe for the vast majority of patients who are susceptible to E. coli or Erwinia L-asparaginases. It also has a plasma clearance delay, which means it doesn't need to be given as often [54]. 31 adult patients were given pegaspargase intravenously (dosages from 500 to 8000 IU/m^2) during a fortnight in a phase-I dose-escalation experiment. Ternary individuals experienced anaphylactic responses as a result of the toxicity. Other significant related hazards were hyperglycemia and hepatic impairment. The study's findings made no mention of a link between medication dose as well as toxicity profile of ALL patients showed signs of improvement [55].

This study served as the foundation for later trials, which used the same dosage range of 2000 to 2500 IU/m^2 for clinical investigations. Patients with consistent ALL were administered a single dose of pegaspargase (2000 IU/m^2/week) for a 14-day exploratory period in a multidisciplinary phase-II open label clinical trial. Following that, a multi-agent chemotherapy regimen consisting of Vincristine, pegaspargase, and prednisone was delivered [56-58]. A multicenter patient with recurrent ALL was treated with a pegaspargase (2000 IU/m^2/ week) across a 14-day exploratory window in clinical trial of phase-II. Following that, vincristine, prednisone, and pegaspargase were given as part of a standard multiagent chemotherapy treatment. Doxorubicin (40 mg/m^2) was also given to patients, with parenteral chemotherapy starting on day 14 [59]. During the 14-day trial period, 22 percent of Pegaspargase patients achieved full or partial remission with monotherapy. After the 35-day induction period ended, 78 percent of patients were able to achieve partial or complete remission [60].

There was no indication of anaphylactic reactions throughout therapy. Mild urticaria and local allergic responses were seen. The frequency of hyperglycemia and pancreatitis was lower than predicted based on previous research using native l-asparaginase. Various organizations have performed randomized studies to assess the safety, effectiveness, and practicality of giving pegaspargase against the standard ALL induction regimen, a native preparation of E. coli L-asparaginase was used [61].

Patents Reported Related to the L-asparaginase

Many patents are available with respect to used therapy as anti-ALL. L-asparaginase therapy is used and has a function in the treatment of cancer. Several patents have already been awarded, with a focus on the pharmaceutical and food industries' usage of L-asparaginase. L-asparaginase activity was increased in biological carrier-based L-asparaginase in vitro and in vivo. As indicated

in Table-4, the ways for treating cell proliferative illnesses with L-asparaginase have enhanced and strengthened the stability action of L-asparaginase. It is patented to convert Pegylated L-asparaginase to L-asparaginase. This compound, which has a longer half-life and higher activity in vitro and in vivo, is being considered as a second-line treatment for ALL patients who have established hypersensitivity to existing L-asparaginase or who have recurrence of ALL after treatment with existing L-asparaginase medicines. The various patents show a decrease in immunogenicity compared to the native form, as well as changes in asparaginase efficacy encapsulated in a mouse pancreatic xenograft model. The recombinant technique has also concentrated on the development of novel asparaginases with superior thermotolerance qualities, such as increased activity at extreme temperatures and greater thermostability (Table. 4.) [62].

Table 4: List of Patents on Asparaginase.

S. No.	Publication Number	Date of Publication	Tittle	Name of Applicants	Authority	References
1	2009/080837	02-07-2009	Asparaginase encapsulated in red corpuscles for treatment of cancer of the pancreas	Erytech Pharma	France	[63]
2	US 2010/0221385 A1	18-01-2011	Asparaginases	Novozymes A/S	Denmark	[64]
3	US 2011/0229984 A1	10-11-2015	Materials and methods directed to Asparagine synthetase and asparaginase therapies	Department of Health and Human Services, USA	United States	[65]
4	US 2020/0347374 A1	05-11-2020	Pegylated L-Asparaginase	Jazz Pharmaceuticals II SAS	France	[66]

Conclusion

Modern chemotherapy regimens that include intensified asparaginase therapy have helped to improve survival rates for patients of all ages diagnosed with ALL. The conventional therapies have severe effects on all the individuals. As a result of the preceding discussion, it is reasonable to conclude that asparaginase is an imperative medicine in the handling of lymphoid malignancy patients. It has become an attractive agent for combination therapy protocols for juvenile leukaemia due to its myelosuppressive nature and lack of side effects. The immunogenic issues connected with the medicine's native forms as well as the requirement for frequent administration, appear to have been resolved with the introduction of PEGylated asparaginase. It is preferable over the native medication because of the ease of administration. Asparaginase has been thoroughly tested and proven to preserve its anti-leukemic effectiveness while requiring less frequent administration than the native substance.

Consent For Publication

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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