



Review

Cladribine: A Therapy Bringing Hope for Relapsing Multiple Sclerosis

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Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune neurological disorder that affects the central nervous system. Its exact cause remains unknown, but it is believed to result from both genetic predisposition and environmental factors. The two MS phases include a progressive phase and a relapsing-remitting phase. Although the mechanisms driving relapse incidence remain unknown, efforts to identify the cause and prevent MS are ongoing. **Methods:** This narrative review summarizes the current evidence of cladribine's role in managing the forms of relapsing MS. A focused literature search of six major databases was performed to identify relevant publications. **Results:** Cladribine has been used as a medication for hairy cell leukemia since 1993, and in 2017, it obtained approval for the treatment of MS in adults. In the treatment of relapsing-remitting MS, cladribine offers three significant benefits. First, it is reported to have a safe profile. Second, it requires only two brief annual treatment courses over two years. Third, it has a low cost. Furthermore, it has gained approval from the National Institute for Health and Care Excellence. **Conclusion:** Cladribine is highly effective against MS progression; it cuts the relapse rates by nearly half. Future research should focus on the long-term effect of cladribine use, specifically on the central nervous system, in the context of MS management.

Keywords: multiple sclerosis; relapsing-remitting multiple sclerosis (RRMS); cladribine; disease-modifying therapy (DMT); immune reconstitution therapy (IRT)



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1. Introduction: Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune neurological disorder. It affects the central nervous system (CNS) and causes inflammation and damage to the myelin sheath, which affects communication between the brain and the rest of the body. This leads to a wide range of neurological symptoms, such as vision impairment, numbness and tingling, focal weakness, bladder and bowel dysfunction, and cognitive impairment [1]. The first formal documentation of MS was by Jean-Martin Charcot in 1868. He described the classical triad of nystagmus, intention tremor, and scanning speech. Since then, diagnostic criteria have evolved, and MS is now recognized as a multifactorial disease influenced by both

genetics and environmental triggers [2–4]. Environmental factors include low vitamin D, smoking, and obesity [5]. Among patients with a genetic predisposition, Epstein–Barr virus infections have been implicated in triggering the disease [5].

There are different types of MS, including relapsing-remitting MS (RRMS), which is the most common form, as well as primary progressive MS (PPMS) and secondary progressive MS (SPMS). Each type has a specific disease pattern [6]. MS is diagnosed primarily through magnetic resonance imaging (MRI), which will show a lesion or plaque accumulation in the brain and spinal cord; cerebrospinal fluid (CSF) also helps in the diagnosis [7]. Now, McDonald criteria are used for the diagnosis, which require dissemination of lesions throughout different parts of the CNS (dissemination in space) and dissemination in time [8]. Despite improvements, diagnosing MS can be challenging, especially in atypical or early cases, because diseases such as neuromyelitis optica or small vessel ischemic disease can mimic MS on MRI, leading to misdiagnosis [9].

Like many different neurological diseases, MS does not have a direct cure, but different treatments help to manage the symptoms and decrease the disease intensity [10,11]. Disease-modifying therapies (DMTs) aim to reduce the frequency and severity of relapses and slow disease progression. These include injectable medications like interferon beta, oral treatments such as dimethyl fumarate, and monoclonal antibodies like natalizumab [12]. There are some treatment challenges, including limited efficacy in progressive forms, side effects, and differences in patient response to DMTs [5]. The prognosis of MS depends on many factors, such as the disease subtype, age, onset, and the response to the treatment, so some patients live with mild symptoms for many years, while others may experience severe symptoms [13]. This review aimed to bring an overview of MS burden, the challenges in its treatment, such as the relapse, and address the new drug Cladribine as a potential treatment for MS. This review describes its history, mechanism of action, and findings from major studies and meta-analyses.

2. Materials and Methods

A narrative review was conducted to summarize the current evidence of the role of cladribine in the management of relapsing forms of MS. A focused literature search was performed in Cochrane Library, Embase, Google Scholar, MEDLINE, and PubMed to identify publications from 2003 to 2025. Search terms included multiple sclerosis, relapsing-remitting MS, cladribine, disease-modifying therapy, and immune reconstitution therapy. Studies were included if they involved human subjects with RRMS or active SPMS, were published in English, and provided clinically relevant information regarding cladribine's mechanism of action, efficacy, safety, comparative effectiveness, or regulatory status. Clinical trials, observational studies, real-world evidence, meta-analyses, and authoritative narrative reviews were considered. Animal studies, non-English publications, unrelated articles, and opinion pieces lacking scientific support were excluded. Titles and abstracts were screened first, followed by a full-text review when appropriate. Reference lists of key articles were also examined for additional relevant studies. Because this is a narrative review, no formal risk-of-bias assessment or quantitative synthesis was performed.

3. MS Relapses and Their Burden

A multiple sclerosis relapse is an acute onset or worsening of neurological symptoms that persists for at least 24 h [14,15] in the absence of fever or infection. It is a new attack of inflammation of the CNS, which results in temporary or sometimes permanent dysfunction. Progression of MS can take place independent of relapses and is termed progression independent of relapse activity (PIRA). However, relapses are most frequent in patients with relapsing-remitting MS (RRMS) and can also occur during the initial period

of secondary progressive MS (SPMS) pattern [14]. The cumulative effect of relapses is referred to as relapse-associated worsening (RAW). Relapses reflect inflammatory activity and are one of the key events that determine the disease course in early MS. It is therefore crucial to identify and treat them efficiently, both in terms of reducing patients' suffering and preventing disease progression.

The inflammatory nature of MS relapses lies in autoimmune-mediated inflammation. Autoreactive T and B lymphocytes cross the blood–brain barrier and trigger a cascade of immune responses against the myelin sheath and axons of the CNS [16]. The consequence is demyelination, axonal injury, and the formation of gliotic scars. B cells, in particular, have been found to play a key role in MS pathology, and B cell-depleting therapies such as ocrelizumab have been clinically effective [15,17].

The current treatment of MS relapses is twofold: treatment of the acute attack and prevention of future attacks. Acute treatment is based on high-dose corticosteroids to reduce inflammation and hasten recovery, but they do not prevent future relapses or alter the disease course [17,18]. Recent evidence supports early initiation of high-efficacy therapies. These agents, comprising monoclonal antibodies natalizumab and ocrelizumab, have shown the ability to reduce relapse rates, MRI lesion activity, and the risk of long-term disability [19]. However, access limitations, potential side effects, and the need for personalized treatment decisions remain primary challenges in relapse prevention.

While some patients completely recover from a relapse, others experience incomplete resolution of symptoms and have residual neurological deficits. The consequence of relapses is far more than symptoms alone. Recurrent attacks can result in cumulative neurologic damage, with effects on vision, coordination, strength, and cognition. Fatigue and cognitive impairment are often worsened by relapses [20], contributing to the cumulative burden on the patient [14,17]. Emotionally, the uncertainty of relapses and the unpredictability of disease progression can be upsetting, and patients are more likely to develop increased anxiety and fatigue [20]. Additionally, relapses often interfere with personal, professional, and social life, with many patients complaining about the inability to maintain jobs or conduct daily tasks [19].

Interestingly, recent studies have emphasized that not only does early aggressive treatment reduce relapses, but it can also delay significant disability milestones, i.e., the need for help in walking. This underscores the value of early treatment in preserving patient quality of life and long-term independence [14,19].

4. Challenges in Treating MS and Preventing Relapses

As a T cell autoimmune illness, multiple sclerosis has two phases: a progressive phase and a relapsing-remitting phase. The adaptive immune system sets off relapses by invading the neurological system with waves of T helper cells. A complicated immunological cascade is triggered, resulting in ongoing inflammation and fresh assaults. The innate immune system drives inflammation-induced neurodegeneration, which results in the secondary progressive phase. One of the main questions in MS research is how to stop this progression. The emergence of MS is attributed to a combination of genetic vulnerability and environmental factors, but T cells can become autoreactive due to unknown antigens from MHC class II molecules, leading to inflammation. Dendritic cells and macrophages play a role, and Na⁺ concentrations affect antigen-presenting cell function and matrix metalloproteinase activity. Current treatments focus on inflammation processes [21].

Many MS patients eventually develop secondary progressive illness (SPMS), even though the majority initially experience relapsing-remitting disease. This shift is believed to be connected to the fact that neurodegenerative processes are becoming more prevalent than inflammatory processes as the main causes of disability. Nonetheless, some people have

primary progressive disease (PPMS) at first, which is typified by a progressive build-up of neurological symptoms followed by a build-up of impairment. The complex and poorly understood pathophysiology of MS in general, and the progressive illness in particular, has made treating both PPMS and SPMS—collectively known as progressive MS—quite difficult [22].

Relapses are a distinguishing characteristic of RRMS. While their diagnostic value is mostly related to the diagnosis of clinically definite MS, their prognostic value is defined by the relatively high probability of partial remission and residual impairment. Although the mechanisms driving relapse incidence remain unknown, various modifiers of relapse risk have been identified, including demographic and clinical variables, many of which suggest chances for improved disease management. Furthermore, relapse phenotypes have been linked to patient and illness features, and an individual's tendency to specific phenotypic presentations may indicate distinct neuroanatomical disease patterns. While immunomodulatory treatments and corticosteroids form the basis of relapse prevention and acute care, respectively, their effect have only been partial [23].

The rate of relapse, short-term disability measurements, and MRI measures of inflammation are all decreased by current MS therapy, but these drugs have little to no effect throughout the progressive or degenerative stages of the disease. Thus, there is a lot of interest in creating novel treatments that try to reverse neurodegeneration [24].

MS therapy must address numerous disease pathways, including proinflammatory T cell suppression, regulatory T cell induction, cell trafficking into the nervous system, axon and myelin protection, and innate immune response modulation. MS therapy is challenging without biomarkers due to its clinical and pathological heterogeneity. Treatment is further complicated by unfavorable side effects produced by immunological suppression [25].

5. Cladribine

During the 1980s, two scientists working at the Scripps Research Institute, Drs. Beutler and Carson discovered the compound cladribine when they incidentally found that a reduction in adenosine deaminase levels led to B cell lymphocyte destruction through the accumulation of deoxynucleotides in the cells. This was typically observed in children with adenosine deaminase deficiency. They hypothesized that cladribine could be used to target B- and T-lymphocytes to treat MS. In 1991, Dr. Beutler collaborated with Dr. Sipe at Scripps, La Jolla, CA, USA to test the drug for aggressive forms of MS and hairy cell leukemia [26]. Cladribine was eventually marketed and manufactured by the Johnson & Johnson corporation, New Brunswick, NJ, USA.

Cladribine was approved by the United States for the treatment of hairy-cell leukemia in 1993. In August 2017, the EMA approved cladribine for treating adult patients with highly active relapsing MS [27]. The FDA approved cladribine for treating RRMS and active SPMS in March 2019, and many other countries followed [28]. Cladribine has also been used for low-grade lymphomas, and in non-Hodgkin lymphoma and chronic lymphocytic leukemia [29].

Cladribine is a synthetic deoxyadenosine analog prodrug that preferentially depletes the lymphocytes that are a fundamental part of the pathogenesis of MS, involving both B- and T-lymphocytes. Targeted therapies against these lymphocytes have been used to reduce the risk of relapses and decrease the severity and progression of some forms of MS [27,28]. Cladribine tablets are an immune reconstitution therapy that selectively targets specific immune cells. It is the first oral therapy for MS with an infrequent dosing schedule that is given for two years, thus decreasing the monitoring burden and improving adherence compared with disease-modifying therapies (DMTs) [27].

Mechanism of Action

Cladribine acts only on adaptive immune cells, sparing the innate immune system. It targets various subtypes of lymphocytes, the most targeted cell type being CD19⁺ B cells. Although the T cell count decreases following treatment with cladribine, both CD4⁺ and CD8⁺ cells show less depletion than CD19⁺ B cells. Studies have confirmed the depletion kinetics of cladribine on proinflammatory immune cell subsets, which include memory B cells and central memory T cells, with a less pronounced effect on cells involved in immunity against pathogens [28].

Cladribine enters targeted cells via specific nucleoside transporter proteins as a pro-drug, and gets converted to its active form, 2-chlorodeoxyadenosine triphosphate (2-CdATP), by deoxycytidine kinase (DCK) catalyzed phosphorylation. This activation is counterbalanced by the reconversion of phosphorylated cladribine into its nucleoside form by 5'-nucleotidase (5'-NTase) [28]. Thus, active cladribine accumulation in targeted cells is directly dependent on DCK to 5'-NTase ratios. This ratio is highest in T cells, B cells, and dendritic cells, and lowest in nonhematological cells, giving the drug its selective nature [30].

As active cladribine builds up within target cells, an overall reduction in the number of these cells can be observed, and it affects both resting and dividing cells. This reduction is due to a disruption in DNA synthesis and repair. Cladribine causes accumulation of single-strand DNA breaks in resting cells, leading to cell apoptosis. In actively dividing cells, DNA synthesis and cellular proliferation are disrupted through the cytotoxic effects of cladribine. These effects on lymphocytes decrease their activity on myelin and nerves, which prevents further neuronal damage and disease progression [30].

Cladribine can be taken with or without food and is rapidly absorbed after oral administration. The oral bioavailability of the drug is approximately 40%. It can reach a mean maximum plasma concentration of 22–29 ng/mL in approximately 0.5 h in fasting patients and 1.5 h when taken with meals [27]. Cladribine has extensive tissue distribution and intracellular uptake either as a parent drug or a phosphorylated metabolite; its mean volume of distribution is large, ranging between 480 and 490 L [31]. This considerable distribution across biological membranes is facilitated by various transporter proteins, including concentrative nucleoside transporter 3 (CNT3) and equilibrative nucleoside transporter 1 (ENT1). Both play a major role in transporting cladribine into lymphocytes. Breast cancer resistance protein (BCRP) and ENT 1 also play a major role by causing cladribine efflux from white blood cells. Additionally, cladribine is able to cross the blood–brain barrier [32].

As mentioned previously, cladribine undergoes phosphorylation by DCK, forming its various metabolites, which accumulate within lymphocytes. Most importantly, its active metabolite CdATP has a 10 h intracellular half-life. However, the unchanged parent drug is the main component present in plasma and urine following both oral and intravenous administration [31]. Reaction phenotype studies show that cladribine is not a relevant substrate to the cytochrome P450 system, and hepatic metabolism accounts for less than 10% of the total clearance [33]. Cladribine elimination occurs equally through both renal and non-renal routes, with 60% of the dose excreted remaining unchanged. Its renal excretion occurs through tubular excretion in addition to the glomerular filtration. Its median renal clearance of 22.2 L/h surpasses the glomerular filtration rate [31]. ENT1 and BCRP facilitate the transportation of cladribine through the basolateral and apical membranes of renal tubular cells, respectively [32]. Non-renal clearance of cladribine occurs through intracellular distribution and entrapment of CdATP within lymphocytes, which then gets eliminated throughout the lymphocyte life cycle with an estimated median clearance value of 23.4 L/h [33].

There are only limited relevant clinical drug interactions with cladribine. Since cladribine is only present for a few days during every treatment year, and since MS is associated with high rates of comorbid conditions, potential drug interactions should be strictly evaluated and avoided during these periods. These drug interactions include any inhibitors of cladribine transporter proteins, such as ENT1 inhibitors (e.g., ticagrelor, dipyridamole, diltiazem, nifedipine, nimodipine), CNT3 inhibitors (e.g., fludarabine, clofarabine), BCRP inhibitors (e.g., eltrombopag), and PDE3 inhibitors (e.g., cilostazol). Furthermore, concomitant administration of drugs that require intracellular phosphorylation should also be avoided with cladribine; these drugs include lamivudine, ribavirin, and zalcitabine [31,33].

6. Cladribine and MS Relapses

6.1. Contraindications

Cladribine is associated with several contraindications that might negatively affect the overall health of a patient, especially pregnant and breastfeeding women, as it is associated with congenital malformations due to possible interference with the DNA synthesis of the baby [28,31]. Thus, pregnancy should be avoided while taking cladribine tablets and for at least 6 months after the last dose. If pregnancy happens, the patient should stop taking cladribine tablets immediately [28]. Similarly, patients with active malignancies should avoid cladribine tablets, and patients with a history of malignancy need to undergo a careful risk-benefit assessment before they begin taking cladribine tablets [30].

Risk of infections is increased while using cladribine because its mechanism of action causes selective lymphocyte depletion, so patients are advised to take some vaccinations, such as the COVID-19 and varicella-zoster virus vaccines, before starting cladribine [28]. However, live or live attenuated vaccinations are contraindicated if the patient is already taking or has taken cladribine tablets until the white blood cell count is within normal limits [30]. Cladribine is also contraindicated in immunocompromised patients, such as patients with HIV or an active chronic infection like tuberculosis [31].

6.2. Adverse Effects

Cladribine is associated with a range of adverse effects (AEs). A common one is skin reactions, including skin rash, hair thinning, transient mucositis, and pruritus [34]. However, these reactions resolve either spontaneously or following treatment with antihistamines and/or steroids [34]. The most common AEs are hematological. These include leukopenia and grade 3/4 lymphopenia, but grade 4 lymphopenia is rare. Lymphopenia is the AE that most commonly leads to treatment discontinuation [35].

Infections are very common AEs. The most clinically relevant infection is herpes zoster (most cases are dermatomal), followed by oral herpes, herpes simplex, urinary tract infections, upper respiratory tract infections, hepatitis B, and pulmonary mycosis [30,35]. Treatment with cladribine tablets could also lead to the development of tumors and malignancies, such as lymphomas (the most common malignancy), uterine leiomyoma, melanoma, basal cell carcinoma, squamous cell carcinoma, and others [30,31,34].

6.3. Superiority Above Other Treatments

Cladribine can be compared to and even replace current treatments due to its unique mechanism of action and advantages over some of the commonly used MS treatments, such as fingolimod and alemtuzumab.

6.3.1. Cladribine vs. Fingolimod

Fingolimod was the first oral treatment approved by the FDA for patients with RRMS to reduce the relapse rate and delay the accumulation of disabilities [36]. Fingolimod

works as an antagonist at a receptor on lymphocytes called sphingosine-1-phosphate (S1P), which inhibits lymphocyte egress from lymph nodes [36]. According to studies, patients taking fingolimod have a higher rate of relapse than patients using cladribine [34,37–39]. Additionally, the number of patients who discontinued treatment due to AEs is higher with fingolimod than with cladribine [36]. In addition, according to the Association of British Neurologists guidelines, cladribine has a higher probability of being effective in comparison to fingolimod [37].

6.3.2. Cladribine vs. Alemtuzumab

Alemtuzumab is used for patients with RRMS who have had no or inadequate response to two or more MS drugs [36]. Alemtuzumab is an anti-CD52 (antigen on lymphocyte and monocyte) monoclonal antibody that is intravenously administered and leads to extended lymphocyte depletion [36]. Both cladribine and alemtuzumab deplete total B cells (at least 90%), and both have a similar level of memory B cell depletion. However, within the first 3 months, naïve B cell hyperproliferation occurs with alemtuzumab, which leads to B cell recovery to 50% over baseline and causes increased risk of secondary autoimmunity [28]. Meanwhile, B cell depletion with cladribine is more consistent and lasting, leading to reduced relapses over 24 months in comparison with alemtuzumab [28]. Patients on cladribine had a lower rate of serious adverse events than those on alemtuzumab. One possible reason is that alemtuzumab depletes T cell numbers by more than 95% (cladribine depletes T cells by 50%), leading to a higher risk of opportunistic infections [28,36].

6.4. Major Trial on Cladribine

Giovannoni et al. and Monif et al. conducted two major trials on cladribine names CLARITY and CLADIN [11,28]. CLADIN was a prospective study by design in phase IV, where they recruited 41 patients with RRMS. They aimed to investigate the main mechanisms of action of cladribine. They assessed its effects on the peripheral monocytes, as well as on the P2X7 receptor. At one week follow-up, the monocyte count was reduced significantly. Furthermore, they reported a reduction in P2X7R pore channel activity, which might suggest a suppression of pro-inflammatory signaling pathways. The CLADIN study demonstrated a novel mechanism of action for cladribine in the treatment of MS by not only affecting the adaptive immunity through the depletion of the lymphocytes but also by activating several mechanisms of innate immunity [11]. On the other hand, the CLARITY trial was a large multicenter phase III randomized, double-blind, placebo-controlled study that included 435 participants and had a follow-up for several years. They reported a significant reduction in relapse rates and disease activity. Patients receiving cladribine had better motility and had less need for future supportive treatment [11,28]. Both studies provide complementary evidence supporting the role of cladribine in MS management. The CLARITY study established the clinical efficacy and long-term benefits of the drug, leading to a rapid and widespread clinical adoption. The CLADIN study provided insights into the mechanistic point of view, as they reported that cladribine can influence both adaptive and innate immune pathways. It is worth mentioning that the CLADIN study was limited by a relatively small sample size and the lack of a control group. On the other hand, the CLARITY study was highly powered and was not designed to fully investigate and understand the biological mechanisms of cladribine responsible for the treatment efficacy of MS. Future studies that integrate clinical and mechanistic outcomes may further clarify how these immunological changes translate into long-term disease control in patients with MS.

6.5. Approval by the United Kingdom and Potential Future Approvals

The National Institute for Health and Care Excellence (NICE) and Merck (Rahway, NJ, USA), the maker of cladribine, previously licensed the drug in the United Kingdom. In

2017, it was the first European regulatory agency to approve the medication for individuals with highly active relapsing MS [40,41]. NICE updated its approval for individuals with active RRMS on March 12, 2025, so cladribine is now available to a broader patient demographic [42]. This approval resulted from the pivotal CLARITY trial, which found that cladribine significantly reduced the annualized relapse rate by 58% compared to placebo ($p < 0.001$). The trial also demonstrated a significant reduction in new brain lesions on MRI [43], and now women can safely conceive in the third and fourth year of their cladribine treatment cycle [42]. Furthermore, it is worth mentioning that the results from the CLARITY trial show improvements in mobility, where most of the people taking cladribine were not using wheelchairs anymore at 3 months of follow-up. The findings of the CLARITY trial showed that people who received cladribine tablets had a lower risk of having their disabilities worsen when compared with people who did not receive cladribine. Furthermore, these patients were less likely to need further treatment for their MS. Also, it is worth mentioning that cladribine is less expensive than other medications and involves less frequent administration and monitoring.

Fenebrutinib and evobrutinib are two potential future treatments for RRMS that are still in phase III clinical trials. Both are oral BTK inhibitors that modulate MS progression by targeting macrophages, microglia, and myelin-attacking B cells. They have been shown to reduce the number of new MRI lesions in people with RRMS [44,45]. While evobrutinib's phase II data showed favorable safety with only colds and transient liver enzyme elevations, fenebrutinib's rheumatoid arthritis study found broader side effects, such as nausea, headache, anemia, and chest infections. Both drugs have cross-therapeutic potential, with evobrutinib being developed for rheumatoid arthritis and lupus, and fenebrutinib currently undergoing phase III trials, which could position it as another useful immunomodulatory option for MS patients [44]. Their shared mechanism of action, BTK inhibition, represents an emerging class of therapies with the potential to significantly expand treatment options for neuroinflammatory and autoimmune diseases [44,45].

In the treatment of RRMS, cladribine offers three significant benefits. Its safety profile is exceptional, with extensive studies demonstrating few major adverse events. It is now authorized for women who are considering becoming pregnant. Plus, it is inexpensive to administer because it only requires two brief annual treatment courses over the course of two years, which lowers costs for both patients and the healthcare system [46].

6.6. Findings from Systematic Reviews and Meta-Analyses

The European Medicine Agency (EMA) accepted cladribine in 2017 for the treatment of extremely active relapsing MS, and the Federal Drug Administration (FDA) approved it two years later for the disease's active form [34]. The EMA approved cladribine for MS treatment based on data from thousands of individuals collected over several years, including participants in clinical trial projects, such as the CLARITY phase 3 trials, ORACLE MS, and the Phase II ONWARD study [43,47].

Numerous clinical trials and meta-analyses have reported on cladribine's efficacy and safety in patients with RRMS. A meta-analysis of 7244 patients in 2023 found a low cancer rate (0.4%), 79% progression-free survival, and 58% relapse-free rate [48]. These findings were supported by a previous 2017 network meta-analysis, which ranked cladribine fourth among DMTs and reported a 58% reduction in annualized relapse rates compared to a placebo, as well as significant improvements in disability [49]. The CLARITY experiment also supported these findings, demonstrating that cladribine reduced annualized relapse rates by 58% (0.14 vs. 0.33 for placebo; $p < 0.001$) and maintained high relapse-free rates (74–85% over 4 years), even in individuals who switched to placebo after initial treatment. Cladribine, which was approved in 2019 for relapsing and active secondary progressive MS

(but not clinically isolated syndrome), is a popular oral treatment option due to its strong disease control, long-term efficacy, and excellent safety profile [50].

When we look at the evidence from these trials and meta-analyses, we see a clear and consistent picture. The data validates that cladribine's 58% reduction in relapse rates is reliable and repeatable in many kinds of patients. More importantly, the data supports its long-term benefits, its high rate of progression-free survival (79%), and quantifies its favorable safety profile, such as a low 0.4% risk of cancer. However, it is worth mentioning that, as stated above in Section 6.2, there are multiple adverse events reported among patients receiving cladribine. For instance, Nabizadeh et al. 2023 conducted a meta-analysis pooling 7244 patients and reported positive results; however, they did not compare cladribine against a different drug but rather did one-arm meta-analyses [48]. Their results showed positive findings, but a future meta-analysis comparing cladribine with other commonly used drugs is needed [48]. Such a comparison was done by Siddiqui et al. 2018 as they performed network meta-analyses, comparing cladribine and disease-modifying treatments [49]. However, a more updated meta-analysis is needed, considering the increased number of recent publications on cladribine.

7. Future Perspectives

Newer DMTs for treating MS are now available, with various mechanisms of action, administration, and efficacy profiles. These therapies are approved for clinically isolated syndrome, relapsing-remitting MS, active secondary progressive MS, and primary progressive MS. However, treatment for progressive forms of MS without activity is difficult, and therapeutic options are limited. Bruton's tyrosine kinase (BTK) inhibitors are being studied in clinical trials for both relapsing and progressive MS. Advances in autologous hematopoietic stem cell transplantation are also being made.

There are worries about the long-term use of more effective DMTs, including the possibility of major infections and cancer, even though the long-term safety profiles for platform injectable DMTs are well-established and verified. Additionally, long-term DMT usage has substantial direct and indirect expenditures, and at a certain age, certain government payers could stop covering DMTs. In this situation, stopping DMTs could be taken into consideration, particularly for elderly individuals whose benefits may no longer exceed their hazards or for those whose illness has been dormant for a long time. However, there are a lot of concerns that make it difficult to determine whether stopping DMTs would be acceptable [51]. Furthermore, the CLADIN trial suggested that future studies should focus on studying the potential benefits of cladribine in progressive forms of MS and other neurodegenerative diseases [11].

Future research should focus on tracking long-term cancer incidence following cladribine treatment to better assess safety over extended periods. Real-world studies are also needed to evaluate treatment continuity, adherence, and clinical results beyond four years. Investigating pregnancy and neonatal effects in women who conceive after cladribine is essential, as current guidance is based on limited data. Additionally, biological-marker research may help identify which patients are most likely to respond positively, ultimately supporting more personalized and successful treatment strategies.

8. Conclusions

Cladribine holds major treatment potential for MS. It has a high safety and efficacy profile. However, further research is needed to establish its long-term safety.

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Abbreviations

The following abbreviations are used in this manuscript:

2-CdATP	2-chlorodeoxyadenosine triphosphate
5'-NTase	5'-nucleotidase
AE	Adverse effect
BCRP	Breast cancer resistance protein
BTK	Bruton's tyrosine kinase
CNS	Central nervous system
CNT3	Concentrative nucleoside transporter 3
DCK	Deoxycytidine kinase
DMT	Disease-modifying therapy
EMA	European Medicines Agency
ENT1	Equilibrative nucleoside transporter 1
FDA	Federal Drug Administration
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
PIRA	Progression independent of relapse activity
PPMS	Primary progressive multiple sclerosis
RAW	Relapse-associated worsening
RRMS	Relapsing-remitting multiple sclerosis
S1P	Sphingosine-1-phosphate
SPMS	Secondary progressive multiple sclerosis

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