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REVIEW

The role of NK and NKT cells in the pathogenesis and improvement of multiple sclerosis following disease-modifying therapies

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Abstract

Background: Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) that T cells become autoreactive by recognizing CNS antigens. Both innate and adaptive immune systems are involved in the pathogenesis of MS. In recent years, the impact of innate immune cells on MS pathogenesis has received more attention. $CD56^{bright}$ NK cells, as an immunoregulatory subset of NK cells, can increase the production of cytokines that modulate adaptive immune responses, whereas $CD56^{dim}$ NK cells are more active in cytolysis functions. These two main subsets of NK cells may have different effects on the onset or progression of MS. Invariant NKT (iNKT) cells are other immune cells involved in the control of autoimmune diseases; however, variant NKT (vNKT) cells, despite limited information, could play a role in MS remission via an immunoregulatory pathway.

Aim: We aimed to evaluate the influence of MS therapeutic agents on NK and NKT cells and NK cell subtypes.

Materials and Methods: The possible mechanism of each MS therapeutic agent has been presented here, focusing on the effects of different disease-modifying therapies on the number of NK and NKT subtypes.

Results: Expansion of $CD56^{bright}$ NK cells, reduction in the $CD56^{dim}$ cells, and enhancement in NKT cells are the more important innate immune cells alterations following the disease-modifying therapies.

Conclusion: Expansion of $CD56^{bright}$ NK cells or reduction in the $CD56^{dim}$ cells has been associated with a successful response to different treatments in MS. iNKT and vNKT cells could have beneficial effects on MS improving. It seems that they are enhanced due to some of MS drugs, leading to disease improvement. However, a reduction in the number of NKT cells could be due to the adverse effects of some of MS drugs on the bone marrow.

KEYWORDS
immunotherapy, multiple sclerosis, natural killer cells, nature killer T cells

1 | INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that is caused by the destruction of the myelin sheath of neurons.[1] Multiple theories have been proposed to explain how progressively MS develops. The first theory stated that an inflammatory process drives brain damage. During the progressive stages of the disease, a microenvironment that is created in the CNS supports and maintains inflammatory cells.[2] According to the second theory, MS begins as an inflammatory disease, and after several years a neurodegenerative process unrelated to inflammatory responses becomes the critical mechanism of disease progression.[3] Thus, MS can be a neurodegenerative disease in which inflammation acts as a secondary and reinforcing response.[4,5] Autoreactive immune cells belonging to the adaptive immune system (Th1 and Th17 and B lymphocytes) are the main players in the initiation of MS after their activation and subsequent passage through the barriers. In recent years the effect of innate immune cells on MS pathogens and experimental autoimmune encephalomyelitis (EAE), the most common model used to induce MS in almost all mouse strains, was given more attention.[6,7]

Most MS treatment procedures are long-time courses with immunosuppressive effects, which leaves patients vulnerable to infections and possibly cancer.[8] Recent approaches for MS treatments have focused on disease-modifying therapies (DMTs) such as interferons, glatiramer acetate, sphingosine-1-phosphate receptor modulators, and monoclonal antibody medications, which contributed to decreased number of MS attacks and less disease progression in many patients. Novel treatments for MS have emphasized inducing tolerance against the target antigens and restoring immune homeostasis, whereas the rest of the body's immune defenses became intact. Until now, the most attention in the field of DMTs has been paid to $CD4^{+}$ Foxp3+ regulatory T (Treg) cells,[9,10] and fewer studies have been done regarding the effect of MS drug agents specifically for NK and NKT cell subtypes. In this review, we aimed to evaluate the influence of therapeutic agents on these cells with a focus on their subtypes.

2 | NATURAL KILLER CELLS

NK cells initiate innate immune responses against virus-infected cells and tumors. They are the primary source of cytokines, such as tumor necrosis factor (TNF-α), GM-CSF, and IFN-γ. In humans, there are two main subsets of NK cells, $CD56^{bright}$ and $CD56^{dim}$ NK cells. $CD56^{dim}$ NK cells are quite mature cells that generate mainly 90% of the NK cells in the peripheral blood. $CD56^{bright}$ NK cells, on the other hand, produce approximately 5% to 15% of the total population of NK cells.[11] The levels of perforin and granzyme A in the granules of $CD56^{dim}$ NK cells are 10 times higher than those of $CD56^{bright}$ NK cells, and this feature potentially increases the cytolytic function of $CD56^{dim}$ NK cells.[12] However, $CD56^{bright}$ NK cells produce more cytokines, including IFN-γ, TNF-α, and IL-10. The low cytolytic capacity of $CD56^{bright}$ NK cells can be attributed to their poor ability to kill target cells because these cells have inhibitory receptor NKG2A and lack activatory killer immunoglobulin receptors (KIR) which are expressed by $CD56^{dim}$ NK cells, and also have low levels of granzyme A and perforin in their granules.[12] These two main subsets of NK cells may have different effects on the onset or progression of MS, which within this review, we discuss their changing numbers in response to the drug agents for the treatment of MS.[13] $CD56^{bright}$ NK cells can suppress the effect of T cells following engagement of NKG2A on NK

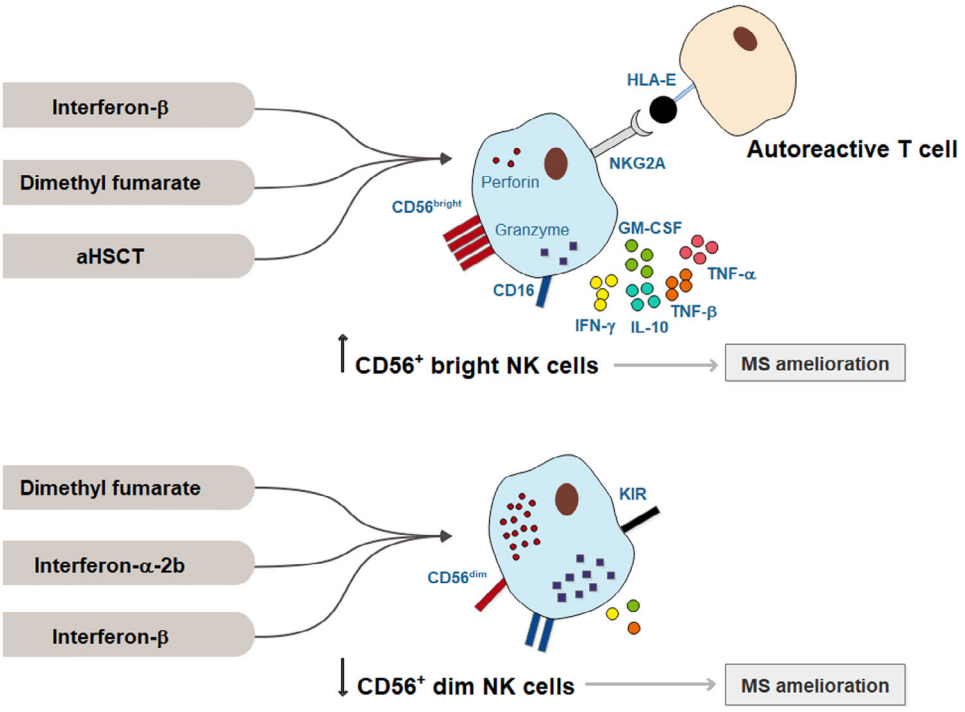

FIGURE 1 The effect of MS drug agents on two main subsets of NK cells. IFN-β, dimethyl fumarate, and aHSCT lead to cause MS amelioration as a result of enhancement in $CD56^{bright}$ NK cell population. On the other hand, IFN-β and dimethyl fumarate along with IFN-α-2b pursue MS amelioration by reducing $CD56^{dim}$ NK cell population

cells to HLA-E molecules on T cells, which seems to be the cause of inflammation during MS.[14,15] In contrast, when CD56^{dim} NK cells are increased by medication, they can be detrimental to the patient.[16,17] Several studies have shown that the elimination and decreased number of such cells influence the improvement of MS.[18-29] However, other studies have revealed that an increasing number of these cells leads to disease recovery.[18,30-60] Alteration of the number and function of NK cells has been reported after treatment of MS patients with drugs and autologous stem cell transplantation as illustrated herein details (Figure 1).

3 | NATURAL KILLER T CELLS

Natural killer T (NKT) cells express T cell receptor and several molecular markers related to NK cells.[61] These cells detect hydrophobic antigens (lipid or glycolipid) presented by CD1d molecules similar to MHC class I.[62] The amount of NKT cells in the blood, peripheral lymph nodes, pancreatic lymph nodes, mesentery, spleen, and liver is between 0.5% and 30% of white blood cells.[63] Natural killer T cells based on the heterogeneity of TCR rearrangement, are divided into two categories of NKT type 1 cells or classical NKT cells or invariant NKT cells (iNKT) and NKT type 2 cells or non-classical NKT cells or diverse NKT cells (vNKT).[10,64] Invariant NKT cells are a unique subset of lymphocytes with significant functional diversity. These cells are vital for the control of autoimmune diseases in the pre-clinical models of MS, type 1 diabetes (T1D), and rheumatoid arthritis (RA). They express the Vα14-Jα18 chain paired with Vβ8, Vβ7, or Vβ2 chains in rodents, or homologous Vα24-Jα18 and Vβ11 chains in humans as the T-cell receptor (TCR) constant chain.[65-68] Contrary vNKT cells express more diverse TCRs than iNKT cells and display innate effector functions and can produce both Th1 and Th2 cytokines.[62,64]

Three subgroups of iNKT cells rapidly secrete a wide range of cytokines due to activation including Th1-related cytokines secreted by Th1-like iNKT cells (IL-12, IFN-γ, TNF-α), Th2-related cytokines secreted by Th2-like iNKT cells (IL-13, IL- 5, IL-4) as well as Th17 cytokines secreted by Th17-like iNKT cells.[69] These cytokines have a multifunctional activity in the body system. The secretion of such cytokines, besides their modulative effects on the adaptive immune system, also provides a protective effect in a wide range of illnesses, including bacterial and viral infections, and autoimmune diseases.[69,70] Human iNKT cells are also divided into CD4$^+$ and CD4$^-$ subsets.[71] Therefore, these diverse subsets would produce different cytokines; the CD4$^+$ iNKT produces mainly both Th1 and Th2 cytokines, whereas the CD4$^-$ iNKT produces Th1 cytokines primarily.[72,73] Studies have shown that CD4$^+$ iNKT cells produce more IL-4 in MS patients than healthy people, but there is no significant difference between MS and healthy people in terms of IFN-γ production by these cells. CD4$^+$ iNKT cells improve MS by diverting immune responses to Th2 cell responses. According to recent studies, there has been a significant decrease in the number and function of iNKT cells, especially CD4$^+$ iNKT cells, in patients with MS. Hence, these

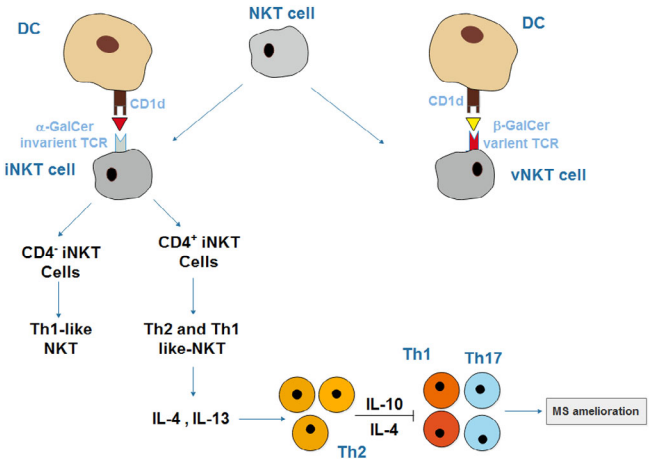

FIGURE 2 Schematic description of NKT cells. The vNKT cells react with CD1d restricted β-Gal Cer and express variant T cell receptors. iNKT cells react with CD1d restricted α-Gal Cer and express invariant T cell receptors. The iNKT cells based on CD4 expression divided into CD4$^+$ and CD4$^-$ subsets, which CD4$^+$ iNKT cells could have immunoregulatory functions in MS

cells play an immunoregulatory role in autoimmune diseases (Figure 2).[71,74-76]

Glycolipid-activated iNKT cells contribute with myeloid-derived suppressor cells (MDSCs) to protect mice against EAE. The cytokines released by activated iNKT cells (IL-4, GM-CSF, and IFN-γ) and molecules from MDSCs (IL-10, arginase-1, and induced NO synthetase) are involved in this protecting effect.[77] Moreover, the α-GalCer increases the immunosuppressive activity of MDSCs in the spleen of mice in which EAE is induced.[77] The protection of these mice against EAE is also associated with the recollection of MDSCs to the CNS. It has been previously shown that attenuated MDSCs reduce the protecting effect of α-GalCer in EAE.[77] On the other hand, the adoptive transfer Of MDSCs from α-GalCer-treated mice improves passive EAE in host animals.[77] Activation of Vα14 NKT cells by α-GalCer glycolipid protects susceptible mice against EAE. The protection provided by α-GalCer against EAE is possible with its ability to suppress myelin antigen-specific Th1 responses or by developing the myelin antigen-specific Th2 responses. Furthermore, α-GalCer is not able to preserve CD1d knockout (KO) mice against EAE.[78]

Diverse NKT cells were shown to have a high tendency to sulphatide, a major component of the myelin sheath.[79] This unique feature of the vNKT cell raised arguments about its role in MS pathogenesis.[79] Sulphatide-reactive CD1-restricted human T cells have been identified in MS patients though it is not yet known whether this T cell population consists of CD1d-restricted NKT cells.[80] Moreover, the vNKT cell expansion in several folds in the mice CNS, suggesting a role of sulphatide as a self-ligand for the activation of vNKT cells.[79] However, in another study, it has been shown that reversed ongoing RRMS was accompanied by sulphatide injection in the immunized SJL/J mice with a proteolipid protein peptide in the EAE model.[81] Thus, vNKT cells regulate the function of iNKT cells and modulate protective immune responses against autoimmunity and inflammation

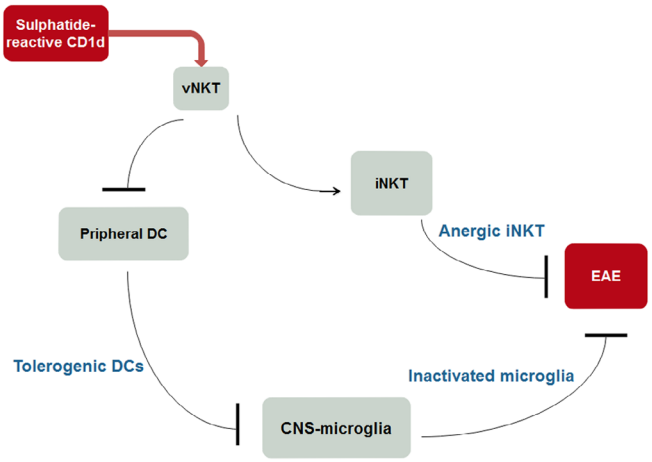

FIGURE 3 The immunoregulatory function of the vNKT cells in EAE suppressing. EAE suppression is a result of iNKT cell activation via sulfatide-reactive CD1d vNKT cells

disease. In this vein, previous studies revealed that sulphatide-reactive vNKT cells induce an anergic response in iNKT cells of C57BL/6 mice.[82] Moreover, iNKT cells were indicated to be required for sulphatide-mediated inhibition of EAE using iNKT cell-deficient Jα18 mice.[81] Similar studies have shown that sulphatide induces tolerance in peripheral DCs and CNS-resident microglia. As a result, tolerogenic DCs could have protective effects against EAE upon adoptive transfer.[83] Collectively, there is an immunoregulatory pathway involving interactions between sulphatide-reactive vNKT cells, anergic iNKT cells, tolerogenic DCs, and microglia in suppressing EAE.[83] (Figure 3). More studies are needed regarding the role of sulphatide-reactive vNKT cells in the progression of EAE. Nevertheless, as discussed earlier, several studies have shown diverse effects of decreased NKT cells during MS and their effects on the incidence and progression of EAE remains unknown.

4 | EFFECTS OF MS DRUGS ON NUMBERS AND FUNCTION OF NK AND NKT CELLS

Table 1 summarizes the effect of different drugs and biological agents used in MS treatment on natural killer and natural killer T cells.

4.1 | Monoclonal antibodies

Daclizumab is a monoclonal antibody and one of the effective drugs in the treatment of MS.[30] It binds CD25 on T cells. It was described that Daclizumab reduces brain inflammation in patients.[31] The treated Patients could benefit from the preferential alteration of innate lymphoid stem cells (ILCs) to CD56^{bright} NK cells due to the usage of this drug.[32] It can lead to the spread of CD56^{bright} NKs.[30] The treated Patients could benefit from the preferential alteration of innate lymphoid stem cells (ILCs) to CD56^{bright} NK cells due to the usage of this drug.[32] Increased activation of CD56^{bright} NK cells during Daclizumab usage could inhibit T lymphocytes.[33] Laboratorial assessments demonstrated that after taking different doses of Daclizumab for some time, CD56^{bright} NK cell numbers had become significantly enhanced, and patients general condition improved.[30-39] Nevertheless, this monoclonal antibody was withdrawn from the market because of causing serious autoimmune encephalitis in MS patients worldwide in 2018.[84]

Natalizumab is also a monoclonal antibody that prevents recurrence in relapsing–remitting MS (RRMS) patients.[45] This antibody targets the alpha chain of the CD49d (VLA-4 integrin) to inhibit cell migration into the tissues such as CSN. It has been shown that the number of NK cells enhanced after taking the medication for 3 to 6 months. However, the NK cells subtype has not been explicitly reported.[45,46]

There are four more monoclonal antibodies including ocrelizumab, ofatumumab, ublituximab, and rituximab that have been considered for MS treatment however they target B cells through CD20 binding.

4.2 | Immunosuppressants

In a study on MS patients treated with *fingolimod*, it has been revealed that patients who were taking the drug had higher NK cells; however, the subtype of NK cell was not elucidated.[47] However, Fingolimod in another study did not show any effect on CD56+ NK cells.[85] A recent finding indicated that Fingolimod did not influence CD56^{bright} NK cells whereas it slightly reduced CD56^{dim} NK cells after treatment.[22] Fingolimod plays its immunosuppression effect via inhibition of lymphocytes releasing from lymphatic tissues. This medication directly affects their function by regulating sphingosine-1-phosphate receptor 1 (S1P1) receptors.[86] RRMS patients who were treated with Fingolimod for 6 months showed an unchanged number of NKT cells compared to healthy controls.[86]

Cyclophosphamide is one of the drugs that can be used for MS treatment in which it suppresses the immune system. In a study on eight MS patients treated with Cyclophosphamide compared to eight other patients who did not receive medication, the activity of NK cells was reduced in treated people.[26]

4.3 | Chemicals

Dimethyl Fumarate (*DMF*) is one of the effective drugs in the treatment of MS. Its effects on the immune system have not been fully elucidated.[23] It was shown that the rate of CD56^{bright} NK cells was increased in MS patients treated with DMF.[48,49] On the contrary, other studies reported no significant difference in NK cell number in MS patients treated with DMF.[87] DMF can impact on CD56^{dim} NK cells. Dias et al demonstrated that DMF increased CD56^{bright} NK cells and decreased CD56^{dim} NK cells.[23] Longbrake et al showed a low number of CD56^{dim} NK cells in MS patients treated with DMF

TABLE 1 Effects of different MS drugs on number of NK and NKT cells

MS drugs	Effect of MS drugs on NK and NKT cells			
	NK cells (in general)	CD56bright	CD56dim	NKT cells
Monoclonal antibodies				
Natalizumab	Increase[45,46]	ND	ND	ND
Immunosuppressants				
Fingolimod	Increase[47]	Decrease[22]/No effect[85]	No effect[22]	No effect[86]
Cyclophosphamide	Decrease[26]	ND	ND	ND
Chemicals				
Dimethyl Fumarate	No effect[87]	Increase[23,48,49]	Decrease[23,24]	Decrease[88]
Linomide	Increase[25]	ND	ND	ND
Laquinimod	No effect[89]	ND	ND	ND
Mitoxantrone	Increase[52]	ND	ND	ND
Ethonafide	Decrease[28]	ND	ND	Decrease[28]
Ibudilast	ND	ND	ND	Increase[91]
Antagonists				
Zauategrast (CDP323)	Increase[55]	ND	ND	Increase[55]
Firategrast	-	Decrease[54]	ND	ND
Cell therapy				
f-tol DC-MOG	Decrease[27]	ND	ND	Increase[27]
Steroids				
Methylprednisolone	Decrease[29]	ND	ND	ND
Testosterone	Increase[98]	ND	ND	ND
Vitamin D3	Increase[57]	ND	ND	ND
Transplantation				
Autologous hematopoetic stem cell transplantation	Increase[59,60]	Increase[58]	ND	ND
Interferon therapy				
Interferon-β	Decrease[18,20]/ No effect[43]	Increase[18,31,36,40-42]/ No effect[43]	Decrease[18]	Increase of iNKT cells[95]/ No effect[18]
Interferon-α	Increase[44]	ND	Decrease[21]	ND

Abbreviation: ND, non determined.

compared with the control group.[24] Lymphopenia is a major concern for MS patients in those who use DMF as a treatment because of an increased risk of progressive multifocal leukoencephalopathy. In a previous study on DMF in MS patients, a decrease in the percentage of NKT cells was observed in lymphopenic patients 6 months after starting the drug usage.[88]

Linomide is known as a therapeutic agent for MS pain. According to evaluations of the effect of Linomide on chronic relapsing autoimmune encephalomyelitis in both MS patients and EAE SJL/J mice, it was able to reverse the clinical signs resulting from being paralyzed and to raise the number of NK cells.[50,51] Andersen et al evaluated the efficacy of this drug in 31 RRMS patients using Magnetic Resonance Imaging (MRI) and showed decreased lesions and reduced number of NK cells in cerebrospinal fluid (CSF) and peripheral blood.[25]

Based on a study on EAE C57BL/6-Ahr$^{tm1.2Arte}$ and Itgax-DTR/EGFP mice, *laquinimod* could act as an NK cells booster.[56] Nevertheless, Lund et al, found that there was no significant change in the relative percentage of a few cell types including NK cells.[89]

Mitoxantrone is one of the approved drugs for the treatment of MS. However, because this drug suppresses the immune system, care must be taken in its long-term usage because it could be with adverse side effects for the patient. In a study that surveyed the impact of this drug on MS, 19 patients with progressive secondary MS were treated with Mitoxantrone. It was observed that the number of NK cells increased, and it could be in favor of improving the disease.[52]

Ethonafide is an anthracene-containing derivative of amonafide that belongs to the azonafide series of anticancer agents.[90] In a study examining the effects of this drug on the EAE C57BL/6 (B6, H-2^b) mice model, it has been indicated that Ethonafide could attenuate the severity and progression of EAE.[28] The therapeutic effects of Ethonafide were associated with a primary reduction in some cells, including NK cells.[28] Adverse side effects of chemotherapeutic agents

such as Mitoxantrone (MIT) in MS patients have led to research on less toxic drugs. Ethonafide is similar to MIT but less toxic. Ethonafide prevents the progression of EAE and improves its severity during the disease.[28] There is a difference between various doses of these two drugs on disease progression. Better outcomes have been reported due to low doses of MIT than Ethonafide, but in high doses, they have the same effects.[28] It seems that the therapeutic effects of Ethonafide come from its ability to reduce NKT cells.[28]

Ibudilast: MS patients treated with Ibudilast, a nonselective phosphodiesterase, showed a significant increase in NKT cells associated with Th2 response in MS and EAE.[91]

4.4 | Antagonists

The *CDP323* efficacy was evaluated in 71 patients with relapsing multiple sclerosis (RMS). Based on the findings, the number of NK cells increased regardless of NK cell subsets.[55] Examination of various doses of CDP323, an oral inhibitor of α4-integrin, showed that the drug increased the number of NKT cells in patients with relapsed MS (RMS) compared to those who received placebo.[55] A study showed that CD3-CD16 + CD56+ NK cells were slightly increased in patients with recurrent MS treated with *firategrast* for 24 weeks.[54]

4.5 | Cell therapy

Tolerogenic Dendritic cells (tDCs) are intended as an immunotherapy option for autoimmune diseases, including MS. The *F-tolDC-MOG* (*VitD3-frozen antigen-specific tol DC + Myelin Oligodendrocyte glycoprotein 40-55 peptide*) is an efficient drug because it can reduce the cost, the variability of performance, and the amount of leukapheresis that should be performed for patients.[27] It was confirmed that the long-term treatment with this drug could reduce NK cells.[27] Treatment with this agent improves the symptoms of EAE. Long-term treatment is effective through activation of immunoregulatory NKT cells.[27]

4.6 | Steroids

Treatment of MS patients with *methylprednisolone* was associated with a reduction of NK cells and improved disease.[29] The effects of *testosterone* have been evaluated in a study with 10 MS patients who were treated with it, and the results of tests showed an increase in NK cells; however, the subtype of NK cells has not been indicated.[53]

Vitamin D3 or Calciferol is mostly used as a supplement for improving physiological activities, but in recent years some therapeutic effects have been described for it. A study using EAE SJL mice revealed that vitamin D3 and monomethyl fumarate (MMF) could activate NK cells.[57] Vitamin D is a very important regulator of the immune system, especially in MS. The active form of vitamin D, known as calcitriol or 1,25-dihydroxyvitamin D3, suppresses EAE. Due to the lack of vitamin D, EAE symptoms are exacerbated, and one of the major targets of vitamin D in EAE is iNKT cells. The deficiency of vitamin D and its receptors can lead to defects in the development of iNKT cells and a decrease in their numbers.[92] Calcitriol is less effective at suppressing EAE in $CD1d^{-/-}$ mice that did not have any of the NKT subtypes and the $J\alpha18^{-/-}$ mice lacking the iNKT than in the wild type mice Furthermore, IL-4 produced by iNKT cells acts as a protective factor and is essential for 1,25-dihydroxyvitamin D3 to prevent the EAE progression.[93] Patients with MS display different symptoms based on the existence of calcitriol. 1,25-dihydroxyvitamin D3 is associated with fewer symptoms. Even in the lack of NKT cells, 1,25-dihydroxyvitamin D3 slightly plays a protective role against EAE. Consequently, vitamin D deficiency is associated with MS.[93]

4.7 | Autologous hematopoetic stem cell transplantation

The use of *autologous hematopoietic stem cell transplantation (aHSCT)* over the past two decades has been suggested as one of the acceptable treatment options for MS. It was revealed that the number of $CD56^{bright}$ NK cells significantly increased in patients with MS treated with HSCT 3 to 6 months after transplantation compared to $CD56^{dim}$ cells.[58] Other studies have also shown that the number of NK cells increases during stem cell therapy.[59,60]

4.8 | Interferon therapy

Interferons α (IFN-α) and β (IFN-β) are considered as another drug for the treatment of MS patients.[94] *IFN-β* in MS patients led to an increase in the number of NK cells in the active phase of the cell cycle (Ki-67+).[40] Several studies have shown that IFN-β in patients, after a certain period, has significantly enhanced the number of $CD56^{bright}$ NK cells. Since an increase in $CD56^{birght}$ NK cells is associated with limited specific immune responses, it can be concluded that the rise in these cells is in favor of patients with MS.[18,31,36,40-42] In another study, IFN-β was used to treat patients with MS who were in the relapsed phase of the disease. In this study, IFN-β increased $CD56^{bright}$ NK cells; however, it reduced $CD56^{dim}$ NK cells, which helps to improve the disease.[18] IFN-β type 1 increases the function and number of iNKT, which protects against disease in MS models. Increased cytokine secretion, including IFN-γ, IL-5, and IL-4, has been observed in patients treated with this drug.[95] Other studies using MS therapeutic agents suggest no impact on NKT cells and no alteration of CD56 + CD3 + NKT cells compared with the onset of IFN-β taking for 12 months.[18]

The efficacy of IFN-α on MS patients has been evaluated in a study, showing activation of NK cells in patients with MS.[44] In a study of six MS patients treated with IFN-α-2b, peripheral blood assessment of patients showed a reduction in $CD56^{dim}$ NK cells after 3 months of treatment.[21] However, after the end of the drug intake, the level of $CD56^{dim}$ NK cells reached the pre-treatment value. The symptoms

have been worsened in five patients and new or larger lesions were observed in four cases.[21]

Although multiple drugs like mitoxantrone, dimethyl fumarate, natalizumab, etc are approved for MS but still decision on MS therapy is difficult because the efficacy of approved drugs are essential to determine that. According to suggestion of Association of British Neurologists (ABN), β-interferons, dimethyl fumarate, and fingolimod are drugs with moderate efficacy for MS (average relapse reduction in 30-50% range) and natalizumab is the one with high efficacy (average relapse reduction substantially more than 50%).[96] In edition, excellent tolerability and a favorable side effect profile is expressed for laquinimod.[97] Overall efficacy of MS drugs according to their immunologic and pathologic pathways of disease is the subject that should be considered by researchers in the future.

5 | CONCLUSION

NK cells initiate an innate immune response to virus-infected and tumor cells and are the main source of many cytokines. In humans, $CD56^{bright}$ NK cells have a more effect on the production of cytokines and regulate immune responses in this way. In contrast, $CD56^{dim}$ NK cells have the potential to be more cytolysis. NK cells are one of the most important and influential cells in the treatment of MS. A few studies have indicated that the removal or deactivation of NK cells improves the course of the disease, while others have suggested that the increase in NK cells improves the condition. A reason for this discrepancy could be the subsets of NK cells that were not fully elucidated. Expansion of $CD56^{bright}$ NK cells or reduction in the $CD56^{dim}$ cells has been associated with a successful response to different treatments in MS. Therefore, $CD56^{bright}$ NK cells may have an immunoregulatory function through increased production of cytokines that decrease adaptive immune responses. $CD56^{bright}$ NK cells can suppress the effect of autoreactive T cells following engagement of NKG2A on NK cells to HLA-E molecules on T cells, which seems to be the cause of inflammation during MS. This function can likely limit autoimmunity. In contrast, when $CD56^{dim}$ NK cells are increased by medication, it can be detrimental to the patient. However, further studies are needed to confirm this and identify possible mechanisms.

Several immune cell abnormalities have been described in MS. The numerical and functional NKT cell changes following immunotherapy have been shown in MS. Decreased number of iNKT in the peripheral blood of MS patients has been confirmed, and the prevalence and function of iNKT cells were restored via the usage of drugs like IFN-β. iNKT cells are involved in the control of autoimmune diseases. The immunoregulatory pathway including interactions between sulphatide-reactive vNKT cells, anergic iNKT cells, and tolerogenic DCs and microglia have suppressing effects on EAE. iNKT and vNKT cells could have beneficial effects on MS improvement. It seems that NKT cells are enhanced due to MS drugs, leading to the disease improvement. Reduced number of NKT numbers could also be due to the adverse effects of MS drugs on the bone marrow. Importantly, different drug dosages could influence NKT-cell changes. However, more studies are required to elucidate the effects of MS drug agents on NKT cells and their variants.

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CONFLICT OF INTEREST

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All authors have read and approved the final version of the manuscript.

The corresponding author, Sanaz Mami had full access to all the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The corresponding author, Sanaz Mami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Because this report involves no experiment, ethics approval is waived.

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