



Targeted Therapy of Multiple Sclerosis: Real-World Experience with Divozilimab

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Abstract

Introduction. Anti-B-cell therapy that prevents clonal expansion of B cells expressing CD20 is a significant achievement in the pharmacotherapy of multiple sclerosis (MS). Randomized studies have shown high efficacy of monoclonal antibodies (mAb), confirmed by a reduction in the annualized relapse rate (ARR), MRI activity, and the risk of disability progression. Divozilimab (DIV) is a humanized afucosylated anti-CD20 mAb with a modified Fc fragment that provides high effector activity.

The aim is to evaluate the efficacy and safety of DIV in patients with various MS phenotypes in real-world clinical practice.

Materials and methods. The prospective study included 43 patients: 24 with rapidly progressive MS, 9 with highly active MS, and 10 with secondary progressive MS with relapses. All received DIV therapy for 6–12 months. We assessed ARR, MRI activity (lesions with contrast enhancement (T1-Gd⁺), new/enlarged T2 lesions), changes in the Expanded Disability Status Scale (EDSS), CD19⁺ B-cell levels, and the safety profile. Data were analyzed before therapy, at 6 months, and at 12 months of treatment.

Results. Over 12 months of therapy, ARR decreased from 1.3 to 0.03; the proportion of patients without T1-Gd⁺ lesions increased from 27.9% to 100%, and new T2 lesions were detected in 6.1%. The median EDSS decreased from 3.0 [2.0; 3.5] to 2.5 [2.0; 3.0]. Profound depletion of CD19⁺ B cells was noted (0% [0.0; 0.2]); NEDA-3 (No Evidence of Disease Activity-3) status was achieved in 84.9%. Adverse events were limited to mild/moderate infusion reactions (30.2% at the first infusion), and no serious adverse events were recorded.

Conclusion. DIV provides rapid and sustained suppression of clinical and MRI activity in MS with pronounced B-cell depletion and a favorable safety profile, justifying its early use in patients with high disease activity.

Keywords: multiple sclerosis; high-efficacy disease-modifying therapies; monoclonal antibodies; afucosylation; depletion; CD20⁺ B-cells

Ethics approval. Prior to enrollment, all patients signed an informed consent form. The decision to prescribe the drug was made by the medical commission of the Russian Center of Neurology and Neurosciences based on indications and absence of contraindications, in strict accordance with the clinical guidelines for the diagnosis and treatment of MS (2022), approved by Ministry of Health of the Russian Federation, and resolutions of expert councils.

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Таргетная терапия рассеянного склероза: пострегистрационный опыт применения дивозилимаба

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Аннотация

Введение. Анти-В-клеточная терапия, предотвращающая клональную экспансию В-лимфоцитов, экспрессирующих CD20, является значимым достижением фармакотерапии рассеянного склероза (РС). Рандомизированные исследования показали высокую эффективность препаратов моноклональных антител (мАТ), что подтверждается снижением среднегодовой частоты обострений (СЧО), МРТ-активности и риска прогрессирования инвалидизации. Дивозилимаб (ДИВ) – гуманизированное афукозилированное анти-CD20-мАТ с модифицированным Fc-фрагментом, обеспечивающим высокую эффекторную активность.

Цель – оценить эффективность и безопасность ДИВ у пациентов с различными фенотипами РС в реальной клинической практике.

Материалы и методы. В проспективное наблюдение включены 43 пациента: 24 – с быстро прогрессирующим РС, 9 – с высокоактивным РС, 10 – со вторично-прогрессирующим РС с обострениями. Все получали терапию ДИВ в течение 6–12 мес. Оценивали СЧО, МРТ-активность (очаги с накоплением контрастного препарата (T1-Gd⁺), новые/увеличенные T2-очаги), динамику Expanded Disability Status Scale (EDSS), уровень CD19⁺-В-лимфоцитов, профиль безопасности. Данные анализировали до терапии, через 6 и 12 мес лечения.

Результаты. За 12 мес терапии СЧО снизилась с 1,3 до 0,03; доля пациентов без T1-Gd⁺-очагов выросла с 27,9% до 100,0%, новые T2-очаги выявлены у 6,1%. Медиана EDSS уменьшилась с 3,0 [2,0; 3,5] до 2,5 [2,0; 3,0]. Отмечена глубокая деплеция CD19⁺-В-клеток (0% [0,0; 0,2]); статус NEDA-3 достигнут у 84,9%. Нежелательные явления ограничивались лёгкими/умеренными инфузионными реакциями (30,2% при первой инфузии), серьёзных нежелательных явлений не зафиксировано.

Заключение. ДИВ обеспечивает быстрое и стойкое подавление клинической и МРТ-активности РС при выраженной В-клеточной деплеции и благоприятном профиле безопасности, что подтверждает обоснованность его раннего применения у пациентов с высокой активностью заболевания.

Ключевые слова: рассеянный склероз; высокоэффективные препараты, изменяющие течение рассеянного склероза; моноклональные антитела; афукозилирование; деплеция; CD20⁺-В-лимфоциты

Этическое утверждение. Все участники наблюдения подписали информированное добровольное согласие перед включением в исследование. Решение о назначении препарата принималось врачебной комиссией ФГБНУ РЦНН при наличии показаний и отсутствии противопоказаний, в строгом соответствии с клиническими рекомендациями по диагностике и лечению РС (2022) и резолюциями экспертных советов.

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by a combination of inflammation and neurodegeneration. According to current concepts, the initiation of the pathological immune cascade occurs peripherally, triggering the migration of activated autoreactive T and B cells across the compromised blood-brain barrier, leading to acute demyelinating lesions infiltrated by lymphocytes and macrophages. As acute focal inflammation subsides, chronic active (smoldering) lesions develop, characterized by peripheral migration of inflammatory cells, persistent microglial activation, and progressive loss of myelin and axons in the central zone [1]. In addition to focal changes, MS exhibits diffuse infiltration of unaffected white and gray matter primarily by CD8⁺ T cells with direct cytotoxic activity, exacerbating diffuse loss of myelin, axons, and neurons. It is now established that the key factor in long-term disability progression in MS is the neurodegenerative component developing in chronic neuroinflammation. Its primary mechanisms include diffuse microglial activation, formation of ectopic meningeal follicles, production of pro-inflammatory cytokines, oxidative stress induced by these cytokines, and mitochondrial dysfunction. The combination of these processes accelerates the rate of brain atrophy progression, which determines disease outcomes [2].

Modern therapeutic approaches are based on the principle of earliest possible initiation of disease-modifying therapies (DMTs), which helps reduce annualized relapse rate (ARR), lesion burden, prevent confirmed disability progression, and decrease the risk of transition to secondary progressive MS (SPMS), ensuring long-term disease control [3]. Medications used for MS treatment include DMTs of moderate or high efficacy. The 2022 clinical guidelines predominantly followed an escalation approach, involving prescription of moderately effective DMTs immediately after diagnosis. In cases of persistent suboptimal response or resistance to first-line therapy (i.e., highly active MS [HAMS]), switching to high-efficacy DMTs (HEDMTs) was recommended. The document identified a special disease course – rapidly progressing MS (RPMS), characterized by unfavorable onset and high risk of early disability. For these patients, an induction approach was employed, involving HEDMT initiation at first clinical manifestations of MS¹. The comprehensive efficacy indicator in MS therapy is achieving NEDA-3 criteria: absence of clinical relapses, MRI activity (new/enlarging T2 lesions or T1-Gd⁺ lesions), and confirmed disability progression. Maintaining NEDA-3 status serves as a marker for both short-term disease control and favorable long-term prognosis [4]. The 2025 guideline revision eliminated the division into first- and second-line therapies. Emphasis shifted to patient stratification by disease activity/aggressiveness, expanding indications for early HEDMT use². Network meta-analysis of RCTs shows mAbs demonstrate superior efficacy among HEDMTs, with reduced ARR and disability progression risks [5].

¹Clinical guidelines. Multiple sclerosis in adults. Ministry of Health of the Russian Federation; 2022. (Document not valid.)

²Clinical guidelines. Pediatric multiple sclerosis. Ministry of Health of the Russian Federation; 2025. URL: https://cr.minzdrav.gov.ru/schema/739_2 (accessed on September 06, 2025).

In recent years, particular attention has been focused on the role of B cells in MS pathogenesis. These cells not only produce autoantibodies but also perform antigen-presenting functions, secrete a wide range of pro-inflammatory cytokines (including tumor necrosis factor- α , interleukin-6, and others), and contribute to the formation of ectopic meningeal follicles associated with cortical demyelination and unfavorable prognosis. Memory B-cells with high activation capacity and long-term persistence play the most significant role in maintaining chronic inflammation [6].

Given this, targeted anti-B-cell therapy preventing clonal expansion of CD20-expressing B cells (Cluster of Differentiation [CD] 20) has become one of the significant achievements in modern MS pharmacotherapy. Although anti-CD20 mAbs do not cross the blood-brain barrier, their peripheral action provides a pronounced clinical effect. Depletion of CD20⁺ B cells leads to reduced antigen-presenting capacity, decreased production of pro-inflammatory cytokines, suppression of T-lymphocyte activation, and reduction of memory B-cell populations, resulting in decreased ARR and reduced risk of disability progression [7].

Among anti-CD20 mAbs used in MS treatment, rituximab [8] was historically the first agent to demonstrate dramatic clinical effects. However, rituximab was not authorized for MS treatment and was used off-label. Subsequently, other representatives of this class were developed: ocrelizumab, ofatumumab, ublituximab, and divozilimab (DIV), each with distinct structural features and effector mechanisms. Based on their structure, mAbs are classified into chimeric, humanized, and fully human types [9]. Chimeric mAbs (e.g., rituximab, ublituximab) contain significant murine sequence components, which increases their immunogenicity, elevates the risk of anti-drug antibody formation, infusion reactions, and hypogammaglobulinemia – a reduction in IgG and IgM levels associated with increased risk of infectious complications [10].

Humanized mAbs (ocrelizumab, DIV) are characterized by a minimal proportion of foreign protein fragments and consequently a more favorable safety profile. Fully human mAbs (ofatumumab) theoretically possess even lower immunogenicity; however, their clinical advantages over humanized mAbs in MS therapy are not always pronounced, as evidenced by the lack of radical superiority in controlling disease activity or reducing the risk of adverse effects [11]. When choosing between humanized or fully human anti-CD20 mAbs, one should consider not only the structural features of the molecule but also the dosing regimen and administration convenience.

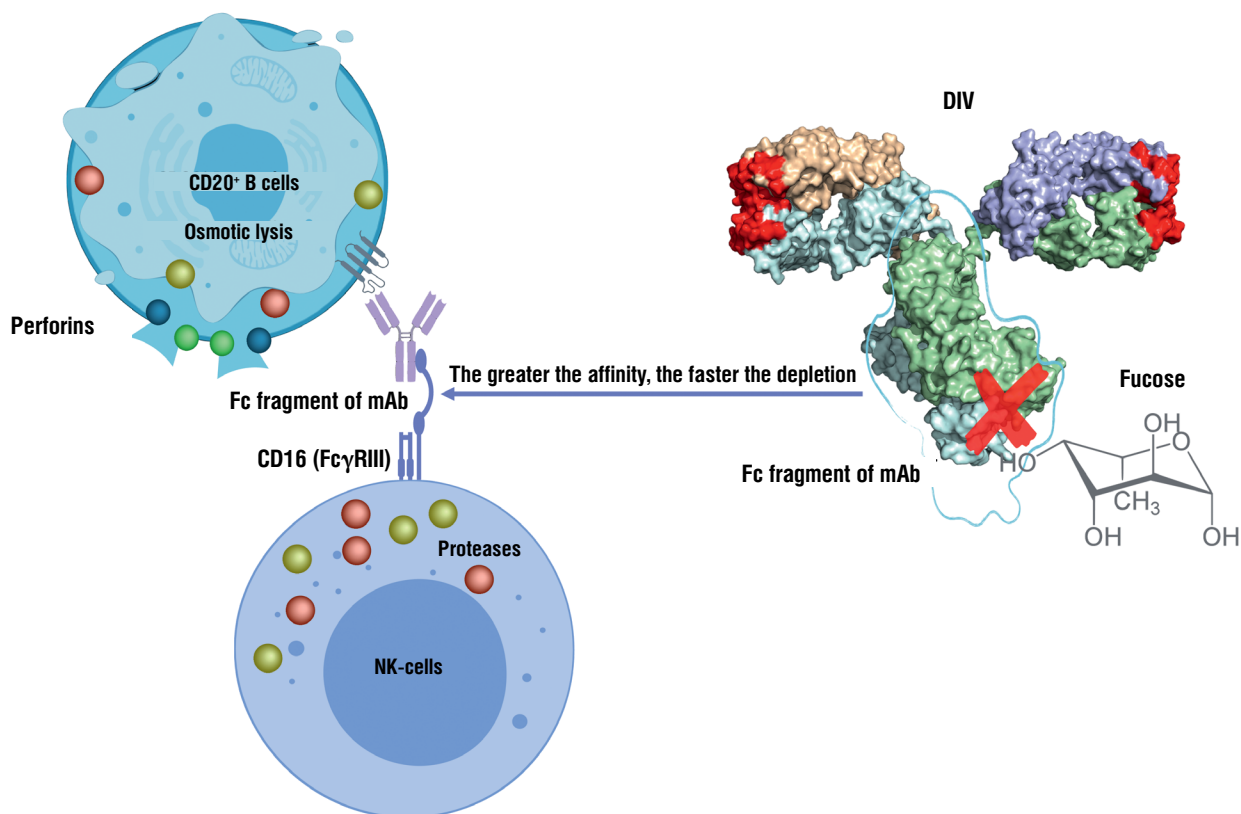
Afucosylated mAbs hold a special place among anti-CD20 agents. Through biotechnological methods during production, modification of the carbohydrate chain in the antibody's Fc fragment is performed by removing fucose from its glycan structure. This modification enhances the effector functions of mAbs. Afucosylated mAbs include ublituximab (not authorized in Russia) and DIV. However, the fundamental difference lies in the fact that ublituximab represents a chimeric mAb, which may potentially limit its tolerability [12]. DIV, in turn, is an advanced third-generation humanized afucosylat-

ed anti-CD20 mAb that combines the advantages of reduced immunogenicity and high efficacy in targeted depletion of B cells [13].

CD20 expression, representing a transmembrane glycoprotein with molecular weight 33–37 kDa, begins at the pre-B lymphocyte stage, persists in immature, mature, and memory cells, but is absent on stem cell precursors and terminally differentiated plasma cells. This expression profile makes CD20 an optimal target for targeted anti-B-cell therapy, as it allows selective elimination of pathogenic clones while preserving the regenerative potential of the humoral immune compartment. The primary mechanisms of action of anti-CD20 mAbs involve effector immune responses activated after antibody binding to target cells. These include antibody-dependent cellular cytotoxicity (ADCC), where the Fc fragment interacts with FcγRIIIa (CD16) on natural killer (NK) cells, leading to immunological synapse formation, perforin/granzyme release, and apoptosis induction in target cells accompanied by serial B-cell depletion; antibody-dependent cellular phagocytosis mediated by macrophages and other phagocytes, where antibody Fc fragments are recognized by Fcγ receptors triggering target cell engulfment and degradation; and complement-dependent cytotoxicity involving complement cascade activation and membrane attack complex formation causing B-cell lysis. Additionally, some anti-CD20 mAbs demonstrate a cross-linking-induced apoptosis mechanism associated with calcium homeostasis disruption and caspase activation [14].

For ofatumumab, the primary mechanism of action is complement-dependent cytotoxicity, while for rituximab and ocrelizumab, it is a balanced combination with ADCC. In contrast, DIV is characterized by predominant activation of ADCC. Experimental studies have shown that afucosylated antibodies provide stronger binding to CD16, enhancing the stability of the antibody-CD16 complex and ensuring more reliable activation of NK cells: reduced recovery time between killing cycles, enabling a single NK cell to sequentially eliminate more CD20⁺ B cells; enhanced intracellular signaling activation leading to increased secretion of cytotoxic molecules (perforin, granzymes) and interferon-γ; improved capacity of NK cells for serial target destruction without compromising effector potential [15]. Thus, Fc-fragment afucosylation ensures ADCC dominance in DIV mechanism of action and more pronounced, sustained depletion of CD20⁺ B cells compared to fucosylated antibodies, considered one of its key pharmacological advantages [16]. The ADCC mechanism is demonstrated using DIV as an example in the Figure.

The analysis of two-year DIV therapy efficacy within the phase III clinical trial BCD-132-4/MIRANTIBUS demonstrated sustained suppression of clinical and radiological disease activity compared to teriflunomide (TFR), confirmed by MRI endpoints (total number of T1-Gd⁺ lesions; count of new/enlarging T2 lesions; T2 lesion volume changes; T1 hypointense lesion volume changes). DIV administration was associated with statistically significant reduction in ARR compared to



The ADCC mechanism of anti-CD20-mAb as exemplified by DIV.

TFR group ($p = 0.0001$). At 2-year analysis post-treatment initiation, ARR was 0.057 in DIV group vs 0.164 in TFR group, indicating 65% relapse rate reduction with DIV (Rate Ratio 0.346; 95% CI 0.202–0.593; $p = 0.0001$). EDSS progression was observed in 18 (10.7%) vs 36 (21.3%) patients in DIV and TFR groups respectively ($p = 0.0075$). The most frequent adverse events were infusion reactions; hematological abnormalities (leukocyte/neutrophil/lymphocyte decreases) occurred rarely. All reported adverse events were expected, mild-to-moderate in severity, resolved without sequelae, and did not lead to treatment discontinuation [17].

Extension study BCD-132-EXT assessed 4-year efficacy/safety of DIV therapy in 44 MS patients. The study enrolled relapsing MS patients previously receiving sequential 500 mg DIV therapy in phase II/III trials. During extended follow-up, patients maintained low ARR values and MRI indicators of inflammatory activity (T1-Gd⁺ lesions, new/enlarging T2 lesions, CUA). DIV safety profile remained favorable and aligned with previous studies and class-related agents [18].

The high efficacy of DIV is further supported by the results of a systematic literature review (PROSPERO protocol ID CRD42022310082) and a frequentist network meta-analysis comparing the 2-year effectiveness of DIV versus other HEDMTs based on data from RCTs. It has been shown that at the 2-year horizon, DIV demonstrates statistically significant superiority over cladribine and fingolimod in reducing ARR, while showing comparable efficacy to alemtuzumab, ocrelizumab, ofatumumab, and natalizumab. DIV achieved the highest surface under the cumulative ranking curve (SUCRA) value of 0.9, indicating a high probability of its superior effectiveness among the compared HEDMTs [19].

To date, real-world clinical practice data on DIV use remain limited; however, available observations generally align with RCT findings [20]. The continued accumulation of post-marketing experience with DIV will help confirm its effectiveness and safety beyond the framework of RCTs.

The aim of this analysis was to summarize the experience with DIV use in patients with MS at the Russian Center of Neurology and Neurosciences, including assessment of clinical-demographic characteristics, changes of disability progression by EDSS scores, disease activity on MRI, frequency of achieving NEDA-3 criteria, pharmacodynamic parameters of targeted B-cell populations, and therapy safety profile.

Materials and methods

From October 2023 to January 2025, DIV therapy was initiated in 43 patients with multiple sclerosis at the Russian Center of Neurology and Neurosciences. The drug product is authorized in the Russian Federation (State Register of Medicinal Products No. 002035 dated March 24, 2023), included in the list of vital and essential medicines and in the “14 High-Cost Nosologies” program, ensuring its wide availability. The decision to prescribe DIV was made by the medical commission of the Russian Center of Neurology and Neurosciences based on indications and absence of contraindications, in strict accordance with the clinical guidelines for the diagnosis and treatment of MS (2022), approved by Ministry of Health of

the Russian Federation, and resolutions of expert councils [21, 22].

Indications for initiating DIV therapy included:

- RPMS characterized by aggressive disease onset with pronounced clinical and MRI activity and high risk of early disability;
- HARMS with suboptimal response or resistance to first-line DMTs;
- SPMS with persistent clinical and/or neuroimaging activity.

At DIV therapy initiation, all patients had stable neurological status assessed by EDSS scale for at least 3 months since last relapse.

Pre-treatment evaluation included: hematology and blood chemistry, serological testing (HIV, hepatitis B/C, syphilis), tuberculosis screening (Diaskintest, T-SPOT.TB, or QuantiFERON), immunological testing for Varicella zoster IgG antibodies, and chest X-ray/fluorography. Contrast-enhanced MRI of brain and/or spinal cord was mandatory within 1 month before treatment initiation. Cancer screening included mammography for women > 40 years or breast ultrasound for younger patients, ovarian cancer markers (CA-125 etc.), and prostate-specific antigen testing for men when indicated. Particular attention was paid to monitoring absolute and relative counts of CD19⁺ B cells considered as key pharmacodynamic markers of anti-B-cell mAb activity. CD20, being the therapeutic target, is expressed on mature naïve B cells and memory cells, but its epitopes may be blocked by the agent itself, complicating laboratory detection. Therefore, CD19 – a pan-B-cell marker expressed on broader B-cell populations (including those with inaccessible CD20) – is used for therapy monitoring. Analysis of CD19⁺ cell changes allows objective assessment of depletion depth and B-cell reconstitution timing during multiple sclerosis treatment [23].

According to the SmPC, the initial dose of DIV was 500 mg administered intravenously via infusion pump as two 250 mg infusions two weeks apart; subsequent administrations were performed at 500 mg every 6 months. To reduce the risk of infusion reactions, standard premedication was used: H1- and H2-histamine receptor blockers were administered one day before and on the day of infusion, intravenous methylprednisolone (100 mg), intramuscular chloropyramine, and oral paracetamol (1000 mg) 30–60 minutes before the procedure. All patients were advised to maintain adequate hydration³.

At the time of analysis, 33 patients had received 3 DIV infusions, while 10 patients had completed only the first 2 treatment courses; the third infusion in this group is planned by the end of 2025. DIV infusions were administered in a hospital setting, with patients under observation during the infusion and for at least 1 hour afterward. Subsequently, regular clinical examinations with disability assessment using the EDSS scale were conducted every 6 months, and MRI of the brain and/or spinal cord was performed annually or when clinically

³Ivizi® (divozilimab). SmPC. Marketing authorization ЛП-№.002035-(PF-RU) of March 24, 2023. Instruction for Medical Use, JSC BIOCAD / PC-137 LLC. URL: https://medi.ru/instrukciya/ivizi_27755/ (accessed on September 06, 2025).

indicated. Laboratory monitoring included assessment of key hematological and biochemical parameters, as well as lymphocyte immunophenotyping with CD19⁺ cell count before each infusion. Treatment safety was evaluated based on the frequency and severity of infusion reactions, changes in laboratory parameters, and other recorded adverse events.

Additionally, the proportion of patients achieving the NEDA-3 criterion (no clinical relapses, no EDSS disability progression, and no MRI activity manifested as new/enlarging T2 lesions and/or T1 gadolinium-enhancing lesions) was calculated.

For analysis, descriptive statistics and paired-sample tests were used – McNemar’s test for dichotomous data and Student’s paired t-test (Welch’s correction) for quantitative data. When necessary, Holm’s correction for multiple comparisons was applied. Quantitative data are presented as median and interquartile range – Me [Q25; Q75]. Qualitative variables are presented as absolute values and proportions of the total cohort (*n*, %). The significance level threshold (*p*) was set at 0.05. Data analysis was performed using R 4.3.0.

Results

The analysis included 43 patients receiving DIV therapy in routine clinical practice at the Russian Center of Neurology and Neurosciences: 23 (53.5%) women and 20 (46.5%) men. The distribution by clinical phenotypes was: RPMS – 24 (55.8%), HAMS – 9 (20.9%), SPMS – 10 (23.3%). In the RPMS subgroup, the gender distribution was equal (women – 50.0%; men – 50.0%). Among HAMS patients, women predominated (55.6% vs 44.4%), while the SPMS group also showed moderate female predominance (60.0% vs 40.0%).

The median age at multiple sclerosis onset (first disease symptoms) in the overall cohort was 27.0 [21.5; 33.5] years (*n* = 43). DMT was initiated at 29.0 [24.5; 36.0] years. The age at first DIV infusion was 33.0 [26.0; 37.5] years. Phenotype analysis revealed HAMS patients had earlier disease onset at 23.0 [21.0; 26.0] years, with consequently earlier DMT initiation (25.0 [24.0; 26.0] years) and first DIV infusion (29.0 [27.0; 30.0] years). HAMS patients developed first symptoms at 29.0 [21.8; 33.3] years, with DMT initiation and first DIV dose administration occurring around the same age (29.0 [24.0; 33.0] and 29.5 [25.0; 34.0] years, respectively). SPMS subgroup manifested later onset at 30.0 [23.5; 36.3] years, with both DMT and DIV infusion initiated at older ages (37.0 [34.0; 39.0] and 39.0 [36.0; 41.0] years, respectively). Characteristics of patients enrolled in the follow-up program are summarized in the table.

In the majority of patients (*n* = 28; 65.1%) in our study, DIV was prescribed as the first DMT. In the RPMS subgroup, the agent was used as first-line therapy in all patients. In the HAMS and SPMS subgroups, DIV was predominantly prescribed as subsequent-line therapy. In patients with HAMS, previous treatment most frequently included interferon-beta, less commonly glatiramer acetate or teriflunomide. One female patient with HAMS was switched to DIV from natalizumab due to increased JC virus antibody titers and a long history of natalizumab therapy (over 3 years). In the SPMS group, previous DMTs also predominantly consisted of in-

terferon-beta therapy; glatiramer acetate was used in individual cases. Six patients (60.0%) received DIV after previous DMT therapy, while 4 patients (40.0%) received it as their first DMT. In patients previously treated with DMTs (*n* = 15), the median time to switching to DIV was 3.0 [2.0; 5.0] years. The shortest interval was observed in HAMS – 2.5 [1.75; 4.25] years. In the SPMS subgroup with relapses, the period before DIV prescription was significantly longer – 5.0 [4.0; 6.0] years. Patients with RPMS received DIV immediately as first-line therapy, therefore the interval between diagnosis and treatment initiation did not exceed 1 year.

Patients who completed 12-month follow-up (*n* = 33) demonstrated a significant reduction in ARR from 1.3 (95% CI 1.0–1.7) in the year before DIV therapy to 0.06 (95% CI 0.02–0.24) and 0.03 (95% CI 0.00–0.21) at 6 and 12 months of DIV therapy, respectively. The proportion of patients without relapses increased from 6.1% (during the year before DIV initiation) to 94% at 6 months and reached 97% by 12 months of follow-up. The changes in the proportion of relapse-free patients at 6 and 12 months compared to baseline status were statistically significant ($p_{6m\ vs\ base} < 0.001$; $p_{12m\ vs\ base} < 0.001$; McNemar’s test). These data indicate rapid and marked reduction in disease activity following the initial administrations of the agent, with sustained effect maintained throughout the first year of therapy.

In the analysis of the entire patient cohort (*n* = 43) prior to therapy initiation, T1-Gd⁺ lesions on MRI were detected in 31 patients (72.1%), while 12 patients (27.9%) showed no signs of MRI activity. After 6 months of DIV therapy, the proportion of patients without T1-Gd⁺ lesions increased to 39 (90.7%). New/enlarged T2 lesions were recorded in 4 patients (9.3%) during this period. MRI activity was separately analyzed in 33 patients after 12 months of follow-up. Prior to DIV therapy initiation, T1-Gd⁺ lesions were identified in 25 patients (75.8%), while 8 patients (24.2%) had none. After 6 months of DIV therapy, activity persisted in only 2 patients (6.1%), and by 12 months, T1-Gd⁺ lesions were absent in all 33 patients. The changes in the proportion of patients without Gd⁺ lesions at 6 and 12 months compared to baseline status were statistically significant ($p_{6m\ vs\ base} < 0.001$; $p_{12m\ vs\ base} < 0.001$). New/enlarged T2 lesions were detected in 4 patients (12.1%) at 6 months, decreasing to only 2 patients (6.1%) by 12 months. The median number of gadolinium-enhancing lesions decreased from 1.00 [0.00; 2.00] (maximum 7) to 0.00 [0.00; 0.00] (maximum 1) at 6 months ($p_{6m\ vs\ base} < 0.001$; Welch’s t-test), with complete resolution in all patients by 12 months ($p_{12m\ vs\ base} < 0.001$; Welch’s t-test).

Analysis of the entire cohort (*n* = 43) with available data pre-DIV therapy and at 6 months revealed baseline EDSS medians of 3.0 [2.0–3.5] in RPMS patients, 3.0 [2.5–3.5] in HAMS patients, and 4.0 [3.5–4.5] in SPMS patients. After 6 months of treatment, median values were 2.5 [2.0–3.0], 2.5 [2.0–3.5], and 4.0 [3.0–4.5], respectively. In the subgroup completing 12-month follow-up (*n* = 33), pre-treatment EDSS medians were 3.0 [2.0–3.5] for RPMS, 3.0 [2.5–3.5] for HAMS, and 4.0 [3.5–4.5] for SPMS with relapses. At 6 months post-treatment, medians decreased to 2.5 [2.0–3.0] in RPMS, 2.5 [2.0–3.0] in HAMS, and remained at 4.0 [3.0–4.5] in SPMS with relapses. By month 12, values stabilized at 2.5 [2.0–3.0], 2.5

Characteristics of patients with MS included in the analysis of DIV efficacy and safety ($n = 43$)

Parameter	General cohort ($n = 43$)	RPMS ($n = 24$)	HAMS ($n = 9$)	SPMS ($n = 10$)
Females, n (%)	23 (53.5)	12 (50.0)	5 (55.6)	6 (60.0)
Males, n (%)	20 (46.5)	12 (50.0)	4 (44.4)	4 (40.0)
Prior DMTs, n (%)	15 (34.9)	–	8 (88.9)	6 (60.0)
No prior DMTs, n (%)	28 (65.1)	24 (100.0)	1 (11.1)	4 (40.0)
Time to DIV initiation, yrs, median [Q_{25} ; Q_{75}]	3.0 [2.0; 5.0]*	–	2.5 [1.75; 4.25]	5.0 [4.0; 6.0]
Time to MS onset, yrs, median [Q_{25} ; Q_{75}]	27.0 [21.5; 33.5]	29.0 [21.8; 33.3]	23.0 [21.0; 26.0]	30.0 [23.5; 36.3]
Time to DMT initiation onset, yrs, median [Q_{25} ; Q_{75}]	29.0 [24.5; 36.0]	29.0 [24.0; 33.0]	25.0 [24.0; 26.0]	37.0 [34.0; 39.0]
Age of the first DIV infusion, yrs, median [Q_{25} ; Q_{75}]	33.0 [26.0; 37.5]	29.5 [25.0; 34.0]	29.0 [27.0; 30.0]	39.0 [36.0; 41.0]

Note. *15 patients who received DMTs prior to DIV. For RPMS time to switch was not calculated since the agent was prescribed as the first-line drug.

[2.0–3.0], and 3.5 [3.0–4.5], respectively. Significant changes were observed in the RPMS group at all timepoints: $p_{6m\ vs\ base} = 0.041$; $p_{12m\ vs\ base} = 0.021$; $p_{12m\ vs\ 6m} = 0.041$, while other MS forms showed no significant changes, potentially due to sample size limitations. Individual dynamics analysis demonstrated stable disease in most patients (62.5%), improvement in 34.4%, and disability progression in only 1 patient (3.1%) with relapsing SPMS.

Additional analysis of MS phenotypes showed that in the RPMS subgroup ($n = 24$), median EDSS scores remained stable (2.5 [2.0–3.0]), with a small proportion of patients maintaining T1-Gd⁺ lesions (4/24) and new T2 lesions (2/24). In patients with HAMS ($n = 9$), there was a trend toward EDSS reduction from 3.0 [2.0–3.5] to 2.5 [2.0–2.5] with complete absence of MRI activity. In the SPMS subgroup ($n = 10$), baseline disability scores were higher (4.0 [3.5–4.3]), decreasing to 3.5 [3.0–4.0] at 12 months, with no MRI activity observed. Thus, the efficacy of DIV therapy in suppressing disease activity and stabilizing neurological status was confirmed across all clinical phenotypes of MS.

Among 33 patients who completed the full treatment course, NEDA-3 was achieved in 28 (84.8%). NEDA-3 was not achieved in 5 (15.2%) patients: due to clinical relapses in 3 cases, MRI activity in 2 cases, and EDSS-progressed disability in 1 SPMS patient.

Pharmacodynamic analysis revealed that DIV therapy was accompanied by marked depletion of CD19⁺ B cells. Baseline median CD19⁺ cell counts were 10.55% [9.22; 13.1] and 199 cells/ μ L [159.5; 243.8]. By 6 months after the first infusion, near-complete disappearance of CD19⁺ cells was observed – 0.0% [0.0; 0.1], 0 cells/ μ L [0.0; 2.0], with sustained effects at 12 months after the second infusion – 0.0% [0.0; 0.2], 0 cells/ μ L [0.0; 2.0]. The changes in both absolute and relative CD19⁺ B-cell counts at 6 and 12 months compared to baseline were statistically significant ($p < 0.001$; Student's t-test).

Adverse reactions were primarily observed during the first infusion (13 patients; 30.2%), less frequently during the second

(5; 11.6%) and third (2; 6.7%). All reported adverse reactions were mild to moderate in severity, did not require therapy discontinuation, and were managed with standard measures.

During therapy, 1 (2.3%) patient exhibited a decrease in total neutrophil count following the second infusion, which was transient and clinically insignificant. In 2 (4.6%) patients, an increase in liver enzyme activity was observed after the first infusion, not exceeding twice the upper limit of normal; subsequent hematological and biochemical parameters normalized.

The most common adverse events (AE) associated with anti-B-cell therapy are upper respiratory tract and urinary tract infections. Study patient interviews did not indicate increased frequency of such AEs. Thus, DIV provided rapid and sustained reduction of CD19⁺ B cells while maintaining satisfactory treatment tolerability.

Discussion

In our study, the median age of MS onset was 27 years, consistent with epidemiological data indicating disease manifestation predominantly in young working-age adults [24]. The initiation of DMT occurred at a median age of 29 years, while the first infusion of anti-CD20 mAb was administered at 33 years, demonstrating an interval between MS onset and escalation to HEDMT. This treatment delay pattern aligns with global clinical practice where patients often start moderate-efficacy DMTs first, escalating to high-efficacy therapies only when signs of high disease activity emerge [25]. Earlier initiation of anti-CD20 mAb therapy is associated with better long-term outcomes and reduced risk of conversion to SPMS [26]. The observed temporal gap between MS onset and anti-CD20 mAb initiation underscores the importance of early treatment strategy selection, reflecting current trends favoring initial high-efficacy therapy. Our findings about differential anti-CD20 mAb initiation intervals across MS phenotypes reflect strategic therapeutic approaches and disease course characteristics. Earlier treatment escalation in patients with HAMS relates

to disease activity persistence and clinical urgency, as endorsed by current guidelines [27]. Conversely, delayed escalation in SPMS patients stems from gradual DMT efficacy loss and postponed treatment decisions. First-line anti-CD20 mAb initiation in RPMS represents a valid approach aligned with induction therapy principles for aggressive MS, supported by long-term efficacy data [28].

The results of this study demonstrate high clinical and radiological efficacy of DIV therapy within the first year of treatment. A marked reduction in ARR and significant decrease in the proportion of patients with MRI activity were observed. Rapid resolution of T1-Gd⁺ lesions and minimal formation of new/enlarging T2 lesions confirm early and sustained control of inflammatory activity in MS. EDSS score changes indicate neurological status stabilization/improvement across all MS clinical phenotypes. In RPMS, median EDSS values remained stable; in HAMS, a downward trend occurred with complete absence of MRI activity; in SPMS with relapses, baseline higher disability levels decreased by month 12 while maintaining clinical and radiological remission.

By month 12 of DIV therapy, 84.8% of patients achieved NEDA-3 status. 15.2% of patients maintained signs of disease activity. Early-treatment relapses likely reflect incomplete therapeutic effect: CD20⁺ B-cell depletion peaks gradually, requiring time for full neuroinflammation suppression [29]. Patients not achieving MRI-based NEDA-3 showed reduced new lesions vs. pre-treatment, suggesting therapeutic benefit and disease transition into less active phase. Only 1 patient showed EDSS progression, likely due to severe baseline defi-

cit, delayed high-efficacy therapy initiation, and limited CNS functional reserve. Individual NEDA-3 failures should not be interpreted as treatment failure. These cases reflect either aggressive baseline phenotypes or insufficient follow-up duration for achieving full therapeutic effect. Continued cohort monitoring will better assess NEDA-3 sustainability.

The obtained data showed that DIV therapy led to rapid and sustained reduction of CD19⁺ B-cell levels, confirming its pronounced pharmacodynamic activity and maintaining depletion throughout the follow-up period, consistent with data from RCTs [17, 30].

DIV therapy demonstrated a favorable safety profile. Infusion reactions, predominantly mild to moderate, were observed mainly during the first infusion, successfully managed without requiring treatment interruption or discontinuation. AEs associated with hematological or biochemical changes were reported in isolated cases and were of mild severity. No increase in infection rates, typically associated with anti-B-cell therapies, was observed.

Conclusion

The use of DIV complied with the provisions of Clinical Guidelines for Multiple Sclerosis Diagnosis and Treatment and the SmPC: it was employed as first-line high-efficacy therapy for RPMS, as well as for HAMS and SPMS with relapses in cases showing signs of suboptimal response or resistance to previous DMTs. In real clinical practice, DIV provided rapid and sustained control of MS activity, combining clinical and MRI efficacy with a favorable safety profile.

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