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PERSPECTIVE

Vaccination Opportunities in Multiple Sclerosis Patients Treated with Cladribine Tablets

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Abstract: COVID 19 pandemic and mass vaccination campaigns have revealed the situation of the most vulnerable patients. In this work, we focused our attention to patients who have Multiple Sclerosis (MS), particularly in treatment with cladribine tablets, trying to understand if and when it is possible to administer the vaccine successfully. In light of the novel topic, we studied the existing literature and analysed experiences with previous vaccinations, such as influenza and VZV, as well as data from countries where vaccination campaigns had already begun. Overall, we have taken into account the mechanism of action, the pharmacokinetic/pharmacodynamic of cladribine, and the changes in the immune system after its administration, together with the preliminary data about the humoral response to influenza, VZV, and SARS-CoV-2 vaccinations in cladribine treated patients. In conclusion, data showed that the use of cladribine tablets seems to permit flexibility regarding vaccination timing and we suggest that vaccination in those patients should be safe and effective.

The current COVID 19 pandemic has re-ignited the interest in vaccines and vaccination procedures. The importance of including fragile individuals has increased as a result of mass vaccination. Millions of patients with multiple sclerosis (MS) around the world are debating whether they can safely receive their vaccine shot with the same efficacy despite receiving immune-modulating or immune-suppressive treatments. In the absence of conclusive empirical data, we will review and discuss the available evidence and the reasonable conclusions for one specific treatment, namely cladribine tablets (Mavenclad).

Keywords: Multiple sclerosis, cladribine, vaccination, safety, efficacy, viral infections.

1. INTRODUCTION

1.1. Vaccination Strategies

The two crucial elements of every vaccination strategy are how antigen is administered and how it induces an appropriate and specific immune reaction [1]. The method to mount an appropriate immune response towards the proposed antigen has relied on decennia on the adjuvants co-administration, substances that alarm the immune system [2].

SARS-COV-2 is a single-stranded RNA virus and belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus* and is comprised of four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). The SARS-CoV-2 virus infects people using the spike protein, which acts as a key allowing viruses to enter cells through the human angiotensin-converting enzyme 2 (ACE2) receptor on human cells. In the anti-SARS-COV-2 strategy, either mRNA or adenovirus vaccines carry on the spike protein sequence [3-5]. Many candidates are being developed [6] but, today, the vaccination strategy is focused on nucleoside-modified RNA or adenovirus vectored vaccines [5, 7-11].

Regardless of the vaccination strategy used, emerging data have shown the importance of humoral and cellular immunity [12].

Although some studies already describe the clinical experience of MS patients with COVID-19 [13, 14], the vaccination within concomitant therapy with oral cladribine raises questions on possible interference with immunization.

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2. MECHANISM OF ACTION OF CLADRIBINE

Cladribine is a deoxyadenosine analog resistant to deamination by the ADA enzyme. The ability to selectively kill proliferating lymphocytes while sparing other tissues led to its use in treating some leukemias before being tested in an autoimmune disease such as MS [15]. The main features of its use in MS are that (i) it is an oral therapy, the only one approved that uses a per kilo dosage of body weight; (ii) has long-term efficacy, at least four years, with a short cycle of administration, repeated after one year [16, 17]. To exert its cytotoxic action, cladribine must be phosphorylated by the deoxycytidine kinase enzyme. This activity is counteracted by the presence of two phosphatases: the 5-'nucleotidase-1A (5NTC1A) and the 5'-nucleotidase-1B (5NTC1B). This balance varies in different cells and is favorable to nucleosidases in all body cells, except for some lymphocyte populations representing the selective targets of cladribine. Also, cladribine may have an immunoregulatory function. T regulatory (Treg) lymphocytes express variable levels of the CD39 molecule, the first enzyme to catalyze phosphohydrolysis of extracellular ATP and ADP towards the generation of adenosine. However, in MS patients, this mechanism is hampered, and reduced levels of CD39 expression by Tregs have been described [18]. In these patients, therapy with cladribine may restore a balance between immunoregulation and self-reactivity. Therefore, we will examine the action of cladribine on the different immune cell subpopulations that are crucial for vaccination.

2.1. Dendritic Cells

Dendritic cells are part of the innate immune system. They represent the most potent antigen-presenting cells, picking up the antigen in the immunization site and migrating to the lymph node to ignite the primary immune reaction. They can be derived from monocytes (monocyte-derived dendritic cells) or directly from the bone marrow (plasmacytoid dendritic cells). Immune-profiling of patients treated with cladribine shows a relative resistance of monocytes to the action of cladribine. A study on a small cohort of patients (n = 50) and with a very unusual treatment scheme (cladribine re-dosing every five weeks for five total cycles) reported the progressive inversion of the relationship between myeloid and plasmacytoid dendritic cells [19]. The latter produce large amounts of IFNalpha and are considered crucial in anti-viral responses. *In vivo* and *in vitro* studies demonstrate an immunomodulatory effect [20] and a short-lived effect of cladribine on dendritic cells [21]. Considering that cladribine is cleared from the body a few days after the last administration and that dendritic cells have a relatively short life span, it is reasonable that a vaccine administration after this time will not worsen the response.

2.2. T Cells (CD4 e CD8)

Cladribine is active in the suppression of T lymphocytes. A small group of patients from the CLARITY study was studied longitudinally with a more refined immuno-profiling allowing the evaluation of different subpopulations of $CD4^+$ T cells [16, 17, 22]. Naïve, effector memory, central memory, Th1 T regulatory CD4+ cells decrease between 40 and 60% in the first 20 weeks of treatment compared to basal levels, showing their nadir between the 13^{th} and 24^{th} week after treatment with cladribine, and then recovering progressively, but slowly, until retreatment without returning to baseline level [16, 17, 22]. A study on the expression levels combined with *in vitro* experiments showed that $CD4^+$ T cells were induced to die by apoptosis by the action of cladribine in a dose-dependent manner [23]. $CD8^+$ T cells are less sensitive to the action of cladribine, with the nadir at 20^{th} week after the treatments and a return to baseline levels within four years. Moreover, there are no significant differences between cytotoxic or memory $CD8^+$ T cells in depletion and repopulation kinetics [22].

However, the mean number of CD4 and CD8 T cells never decreases below the lower limit of normal (LLN) after the first cycle. After the second cycle, only CD4 decrease under the LLN and CD4+ levels recover more slowly, but without evidence of opportunistic infection risk than would be expected from long-term T cell reductions [16]. These data suggest that T cell mediated responses against viral infection and vaccination may be maintained with cladribine treatment.

2.3. B Cells

The depletion of total B lymphocytes following cladribine administration is rapid and very profound with a two-month nadir. Equally steep, however, is the repopulation with a return to reference levels within six months. After re-dosing of cladribine, kinetics are entirely superimposable. At the third and fourth-year, we observe values at the pre-treatment baseline levels [23]. The kinetics of the memory B lymphocytes subpopulation is very different from the total. Value remains very low up to one year after treatment and even after retreatment in the second year. Immature and mature B lymphocytes, on the other hand, are significantly increased, demonstrating how the repopulation of the B cell compartment occurs in the different subpopulations. The germinal center cells that should repopulate the memory B lymphocyte compartment are susceptible to the drug's cytotoxic action, explaining their persistent depletion. On the other hand, this reactivity of B lymphocyte subpopulation to cladribine reassures the possibility of mounting primary B cell responses due to a low ratio of DCK: NTC5C1A/1B in plasma cells; moreover, in 18 MS patients treated with cladribine tablets, absolute changes in CD19+CD138+ and CD19−CD138+ cells were statistically not significant and consequently, treatment did not induce substantial changes in the proportions of antibody-producing B cells [24] but raised concerns on the potential to sustain acquired memory in the long term

3. CLADRIBINE AND VACCINES

Can we hypothesize a good response to vaccines and, in particular, to SARS-CoV-2 in MS patients treated with cladribine?

At the last ACTRIMS meeting, results from two ongoing studies focusing on influenza vaccine protection in cladribine treated patients who received the vaccine after different timing from the drug administration were presented [25, 26].

The first study, MAGNIFY-MS [27], studied the response to the flu vaccine retrospectively because 12 patients received this vaccine as a standard of care. Two control blood samples (baseline before starting cladribine and closest sample available just before vaccination) and two samples post-vaccination were examined. Quantitative antibody titers in response to seasonal influenza vaccine were measured by HAI (Hemagglutination Inhibition Assay with defined seroprotection ≥40).

The majority of these patients had seroprotective antibody titers even before vaccination, and post-vaccination seroprotective titers were maintained. In detail, nine out of 12 patients exhibited a ≥2-fold titer increase, and 4 of them exhibited a ≥4-fold increase for at least one strain of influenza; titers were increased to a greater extent for A influenza strains than B. Overall maintenance of seroprotection or increase in seasonal influenza titers occurred both in patients "early" vaccinated (1.5–6 months at year 1 and 1–4.5 months at year 2 after cladribine treatment) and "late" vaccinated (8.5–10.5 months at year 1 after cladribine). Seroprotection was maintained or increased irrespective of lymphocyte count. Additionally, this analysis also investigated, in three patients, the persistence of immunoprotective response to VZV vaccination performed prior to cladribine treatment. The results showed that all patients maintained antibodies to VZV above seroprotection levels irrespective of their lymphocyte count up to 6 months after cladribine treatment.

The second study is the CLOCK-MS [28], an open-label, randomized, multicenter, Phase IV study in 50 patients with relapse remitting or active secondary progressive multiple sclerosis (RRMS or SPMS). Four patients were included in the vaccine sub-study and received the influenza vaccine as part of standard care.

Blood samples were collected within 21 days pre-vaccination and at four weeks and six months post-vaccination.

The data collected for 3 out of 4 patients showed that these subjects reached protective antibody titers against seasonal influenza four weeks post-vaccination. Two patients had lymphopenia: grade 1 4 months prior vaccination and grade 2 2 months prior vaccination, respectively.

A series of case reports of cladribine-treated MS patients who contracted SARS-CoV-2 across Europe showed that these patients were able to mount an antibody response against the virus, independently from their lymphocyte count during the treatment with cladribine. Moreover, all infections were resolved without sequelae [29-31]. In the post approval safety data (18.463 patients), there was no evidence of increased risk of respiratory viral infection in patients treated with cladribine tablets [17].

The overall preliminary data of these two ongoing studies concerning a few patients [18] and with other limitations (retrospective study, presence of antibodies titer before vaccination, and the missing evaluation to a neoantigen as a control) showed a response to influenza and VZV vaccine in patients treated with cladribine with different timing from the last dose and, of note, seroprotection was maintained or increased irrespective of lymphocyte count at the time of vaccination.

A recent paper reported that 23 cladribine-treated MS patients received the PfizerBNT162b2-COVID19 vaccine with different timing from the Cladribine treatment (all of them after at least four months). All patients developed a protective humoral immune response to the vaccine comparable to untreated MS patients (n=32) and healthy subjects (n=47) independently of the lymphocyte count. No data are available on T cell-mediated immunity in this cohort of patients [32].

These data clearly show that patients treated with cladribine tablets can mount an antibody response to vaccines against influenza, VZV, and SARS-CoV-2 viruses.

4. DISCUSSION

The only way to escape from this pandemic is a mass vaccination and according to the latest update of the Italian recommendations SIN-AISM, all people with MS should get vaccinated to reduce the risk of COVID-19. Moreover, for people treated with cladribine, vaccination does not require a modification of therapy [33].

After considering the newly available data, the MS National Society (US) [34] suggests "getting fully vaccinated 2-4 weeks prior to starting cladribine tablets". For patients on treatment, "the currently available limited data does not suggest that timing of the vaccine in relation to the cladribine tablets dosing is likely to make a significant difference in vaccine response."

CONCLUSION

Given the data discussed above, our clinical question is, "what is the time window to obtain a "good response" to the vaccines in MS patients treated with cladribine tablets?".

Considering preliminary data shown so far, the use of cladribine tablets seems to permit flexibility regarding vaccination timing. However, current knowledge does not establish the efficacy of vaccines in people receiving immunosuppressants for MS or other autoimmune diseases. Particularly with the mRNA vaccines, the immunization seems to be remarkably strong in subjects with a healthy immune system. This brings a note of optimism and reinforces the idea that "some degree of immunity is better than no degree of immunity" [35].

In accord with these premises, the recommendations of scientific societies and patient-advocacy organizations agree upon the general suggestion that PwMS should be vaccinated against COVID-19 as soon as the vaccine is available to them.

Overall taking into account the mechanism of action, the pharmacokinetic/pharmacodynamic of cladribine and the changes in the immune system after its administration, to-

gether with the preliminary data about the humoral response to influenza, VZV, and SARS-CoV-2 vaccinations in cladribine treated patients, our suggestions are:

1. A cautious and prudential approach while waiting to collect new data on ongoing prospective studies with a larger population for a complete evaluation of the immune responses to SARS-CoV-2 vaccine.

2. If the vaccination campaign accelerates, the patients should be advised to receive the vaccine independently of the timing of the cladribine treatment. Seroprotection can be evaluated after vaccination.

3. Currently, scientific societies recommend administering mRNA vaccines in fragile populations such as MS. This recommendation maybe altered in the near future due to new comparative data, both from clinical research and real-world evidence.

Even for patients who have to undergo treatments for MS, the vaccine is the only way out of the epidemic tunnel. Based on the available data, we suggest that vaccination is safe and effective for cladribine-treated MS patients.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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