Commentary

Cladribine: Off-label disease modification for people with multiple sclerosis in resource-poor settings?

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Abstract

Background: A considerable number of people with multiple sclerosis (pwMS) live in low- and middle-income countries (LMIC), where lack of resource adversely affects access to effective disease-modifying treatment.

Objective: The objective of this commentary is to propose a useful cost-effective disease-modifying treatment option for pwMS in LMIC with potential high efficacy and high convenience to the pwMS and treating physician.

Viewpoint: We propose using generic 2-chloro-2'-deoxyadenosine (cladribine), a small molecule licensed for treatment of people with hairy cell leukaemia, as a solution of this significant equity imbalance. Cladribine has been shown in phase II and III trials to be a highly effective disease-modifying treatment for pwMS, and its adverse effect profile is comparable with any DMT currently licensed in high-income economies where an oral preparation has recently been licensed by the European Medicines Agency.

Conclusion: Our viewpoint takes into account experience we have gathered over the past three years in the use of generic cladribine to treat pwMS. Whilst here we focus on MS, there is significant potential for use of cladribine in other conditions that could benefit from its mechanism of action.

Keywords: Cladribine, disease-modifying treatment, low- and middle-income countries, multiple sclerosis, off-label

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Introduction

Although a gradient of increasing risk from the equator is well established, multiple sclerosis (MS) is a truly global disease. The prevalence of MS broadly maps onto the wealth of nations, with 108–140/100,000 people with MS (pwMS) in Europe and North America, compared to 2/100,000 in sub-Saharan Africa and East Asia. However, there may be significant ascertainment bias under-estimating the true prevalence of MS in low- and middle-income countries (LMIC), as there is close to a 100-fold difference in the availability of magnetic resonance imaging (MRI) scanners between the Western Pacific (0.35/100,000) and Africa (0.004/100,000). This makes it difficult to apply the most recent diagnostic criteria, involving imaging. Furthermore, MS is often more commonly diagnosed in traditionally low-prevalence territories once resource barriers are removed, though other factors also contribute to increasing prevalence of MS in LMIC. Although a diagnosis of MS is significant wherever people live, the implications for disease-modifying treatment (DMT), or lack thereof, can be quite different for pwMS living in LMIC. Current DMT guidelines are fundamentally driven

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by the need to balance benefits (including health economic considerations) and risks of DMT licensed by regulatory authorities. However, such guidelines are arguably of limited use in LMIC, where the lack of tax-funded or insurance-based healthcare systems and different health care priorities significantly impact on the availability of DMT to pwMS. The lack of resource not only affects the funding of drugs, but also their application and monitoring of efficacy and, importantly, their adverse effects. We describe a possible solution for pwMS living in LMIC, using injectable 2-chloro-2'-deoxyadenosine (cladribine) to control MS disease activity.

The importance of early effective disease modification

Although the clinical presentation in the majority of cases is characterised by relapses and variable degrees of remissions, MS leads to accelerated loss of brain tissue from onset across all phenotypes, including progressive MS. Due to the significant impact of untreated MS on neurological-function and the quality of life of pwMS, and the cost to society, use of DMT has become a standard in healthcare settings with a high prevalence of MS and ability to fund treatment.

A key problem of treating MS in LMIC is access to DMT

A number of factors may play a role in delaying access to DMT, including low prevalence and therefore lack of familiarity among healthcare professionals. Moreover, diagnostic-support (MRI) is often in short supply. However, drug costs are, without doubt, a critical factor inhibiting access to effective DMT, especially when the mean annual income of pwMS is well below the mean annual cost of DMT (Table 1). The annual estimated cost for MS-DMT in the United States is currently in excess of $10 billion and in the European Union annual costs range from about €10,000 to > €65,000 per person. However, unlike most developed countries, where insurance cover or national health care schemes are the norm, high-cost DMTs are often beyond the financial reach of pwMS. In about 50% of Latin American countries, fewer than 35% of pwMS have a healthcare plan covering DMT, and where DMT is available, it is often restricted to the original, low-efficacy drugs.

Off-label use of drugs to modify the course of MS

Before interferon beta-1b became the first DMT licensed to treat MS in 1993, off-label treatment was commonplace. An incomplete list of off-label treatments that have and are being used to treat pwMS includes: azathioprine (Table 1(b)), cyclophosphamide, intravenous immunoglobulin, methotrexate, mycophenylate, plasma exchange, rituximab (Table 1(b)), mitoxantrone (Table 1(b)) and haematopoietic stem cell therapy. Most cytostatic agents, such as mitoxantrone and cyclophosphamide, non-selectively, target dividing cells and as such have many off-target adverse events such as gastrointestinal problems, hair thinning and potentially sterilisation, which limit their use. Mitoxantrone is probably a highly active DMT, but it is actively excluded from the central nervous system (CNS) by drug-exclusion pumps and importantly carries a significant risk of cardiotoxicity and leukaemia, which is un acceptably high and limits its value in MS. Haematopoietic stem cell therapy can have a significant risk of infection-related mortality. However, the evidence underpinning use of these treatments in pwMS varies in quantity and quality. Furthermore, some agents such as azathioprine may offer limited value, due to low efficacy. However, cladribine stands out in that class I evidence has demonstrated high efficacy and it appears to act similarly to alemtuzumab, ocrelizumab and natalizumab, although such evidence is not definitive in the absence of direct comparative studies. Occasionally, off-label DMTs are widely used even in developed countries, such as Sweden, where over 25% of pwMS receive rituximab. Cladribine may offer a new alternative, given that rituximab still remains a high-cost alternative (Table 1(b)).

Cladribine

Cladribine was licensed in 1993 for the treatment of hairy cell leukaemia and is used to treat other B cell lymphomas. Cladribine is a chlorinated analogue of adenosine that is resistant but not insensitive to adenosine deaminase, which regulates purine metabolism. Cladribine is phosphorylated to produce toxic moieties that kill dividing and non-dividing, T (CD4>CD8) and notably B lymphocytes, due to their selective-expression of deoxycytidine kinase, more limited adenosine deaminase expression and relative lack of some dephosphorylating, cytoplasmic 5’ nucleotidases. Common to other effective therapies in MS and other autoimmunities such as neuromyelitis optica (NMO), arthritis and systemic lupus erythematosus, cladribine induces long-term depletion of memory B cells, probably due to their slow repopulation from lymphoid tissues. This may block release of oligodendrocyte...
Table 1. Estimated global distribution of MS where per capita gross national income is less than the annual cost of expensive DMT and the cost of MS-DMT.

| (a) Countries | Annual income (US$) | Number of pwMS | Prevalence/100,000 |
|---------------|---------------------|----------------|-------------------|
| Africa        |                     |                |                   |
| South Africa  | 6080                | 3500           | 5                 |
| Kenya         | 1340                | 400            | 1                 |
| Libya         | 380                 | 350            | 5.9               |
| Middle East/North Africa |       |                |                   |
| Algeria       | 4180                | 7000           | 20                |
| Morocco       | 3030                | 700            | 20                |
| Jordan        | 4689                | 2500           | 39                |
| Europe        |                     |                |                   |
| Turkey        | 9950                | 40,000         | 55                |
| Hungary       | 12,970              | 20,000         | 62                |
| Romania       | 9510                | 6000           | 30                |
| Latin America |                     |                |                   |
| Brazil        | 9990                | 30,000         | 15                |
| Mexico        | 9710                | 15,000         | 15                |
| Argentina     | 12,450              | 8000           | 18                |
| Asia          |                     |                |                   |
| India         | 1590                | 85,000         | 7                 |
| China         | 7900                | 20,000         | 1.5               |
| Sri Lanka     | 3800                | 1000           | 4.9               |
| (b) Drug name | Brand name          | Illustrative   | Illustrative      |
|              |                     | UK price ($)   | US Price ($)      |
| Cyclophosphamide<sup>a</sup> | Cytoxan           | 332            | 6754              |
| Low efficacy  |                     |                |                   |
| IFNβ-1a       | Rebif               | 14,683         | 91,307            |
| IFNβ-1a       | Avonex              | 11,808         | 85,167            |
| IFNβ-1b       | Betaseron           | 10,163         | 89,133            |
| Glatiramer acetate | Copaxone          | 9305           | 89,131            |
| Teriflunomide | Aubagio             | 18,790         | 88,721            |
| Azathioprine<sup>a</sup> | Imuran            | 150            | 714               |
| Moderate efficacy |                   |                |                   |
| Dimethyl fumarate | Tecfidera       | 24,858         | 92,378            |
| Fingolimod    | Gilenia             | 26,615         | 98,536            |
| High efficacy |                     |                |                   |
| Natalizumab   | Tysabri             | 20,403         | 83,986            |
| Alemtuzumab   | Lemtrada            | 39,138<sup>b</sup> | 91,072<sup>b</sup> |
| Oral cladribine | Mavencefclad       | 39,807         | Not available     |
| Cladribine<sup>a</sup> | Leustatin       | 1330           | 1815              |
| Mitoxantrone<sup>a</sup> | Novantrone     | 429            | 908               |
| Rituximab<sup>a</sup> | Mabthera        | 4851           | 3807              |

(a) The estimated global distribution of MS in the top three countries in each continent and annual income in each region. The figures were based on the Atlas of MS and the World Bank Report. (b) Price of MS-DMT for 70 kg individual based on UK cost and the US pharmacy over-the-counter cost (US$. www.drugs.com, accessed March 2018).

<sup>a</sup>Off-label use.

<sup>b</sup>Average annual cost from two treatment cycles. UK/US prices converted as US$1 = £0.72 March 2018.

MS: multiple sclerosis; DMT: disease-modifying treatment; IFNβ: interferon beta; pwMS: people with multiple sclerosis; UK: United Kingdom; US: United States.
and neurotoxic molecules, formation of ectopic follicles in the central nervous system, and antigen presentation and activation of T cells, and may kill cells harbouring Epstein Barr virus, which is a potential aetiological trigger of disease. Furthermore, unlike any other MS-DMT, cladribine also penetrates into the CNS to deplete cells within the target tissue. These features contribute to the all-round benefit of this agent over other current MS treatments and includes (i) high efficacy of the licensed product (reduction of the annualised relapse-rate by 58% and of the risk of disability progression by 47% over 96 weeks, compared to placebo); (ii) safety that is comparable or better to similar drugs with high efficacy; (iii) excellent tolerability; (iv) selective immune reconstitution therapy, requiring only a short treatment cycle with rapid elimination, potentially enabling drug-free pregnancies. This also allows the potential to explore combination therapies without drug-drug interactions via layering of neuroprotective and symptomatic treatments on top of immunotherapy; and (v) convenience of administration with few monitoring requirements. A further benefit of cladribine as a prime DMT-candidate in a number of LMIC is the fact that NMO may be as common as MS in regions such as South-East Asia. Given its complementary mechanism of action, any adverse effects of cladribine in patients with NMO who have been misdiagnosed as having MS are unlikely, in contrast to other DMTs that exacerbate NMO. However, it is important to consider that people with MS in LMIC may encounter different types of infectious agents and pathogens, such that efficacy and side effects may be distinct from people living in developed countries. Neurologists and people treated with cladribine should be vigilant and report adverse events. Importantly, neurologists should consider enrolling individuals into national and international registries. As such, we currently require all recipients of off-label cladribine to be enrolled with the United Kingdom (UK) MS Register (www.ukmsregister.org).

Off-label cladribine in not-so-resource-poor healthcare settings

Even in affluent healthcare settings, cost-effectiveness considerations often restrict access to DMT. This applies, for example, to pwMS with higher levels of disability, or with less than two documented relapses over the past two years. Based on its favourable risk/benefit profile, we have used subcutaneous cladribine in a number of pwMS who in our healthcare setting, the UK National Health Service, were not eligible for a licensed DMT. In developing our treatment schedule (Figure 1), we took into account both the bio-availability of injectable (100%) versus oral (42%) cladribine, and concerns raised by the European Medicines Agency in their negative assessment in 2010–2011 of oral cladribine. First, we undertook a meta-analysis of phase III trial data, comparing the incidence of cancer among all DMTs licensed by 2015 with the pivotal trial of oral cladribine and detected no risk difference among all DMTs. Secondly, to avoid lymphopenia grades 3 and 4, we decided to adapt the dose administered to individual lymphocyte count. The safety of this agent was subsequently further supported by the licensing of oral cladribine prodrug following re-assessment of safety data in 2017. Since 2014, we have treated over 150 pwMS using

**Figure 1.** Dosing of subcutaneous (s.c.) cladribine according to individual total lymphocyte count.

**Cycle 1**

At week 1 cladribine 10 mg s.c. is administered on three consecutive days (four days in patients >90 kg body weight). Subsequent administration in week 5 is based on total lymphocyte count detected in week 4:

- **If lymphocytes are >1 x 10^9/μl:** Administer 10 mg s.c. on three consecutive days.
- **If lymphocytes are 0.8–1 x 10^9/μl:** Administer 10 mg s.c. on two consecutive days.
- **If lymphocytes are 0.5–0.8 (x 10^9)**: Administer 10 mg s.c. on one day.
- **If lymphocytes are below 0.5 (x 10^9):** Administer no further dose.

**Cycle 2**

At week 48 total lymphocyte count is being tested. If total lymphocyte count is ≥1 x 10^9/μl, cladribine s.c. will be administered identically to weeks 1 and 5 above.

- **If total lymphocyte count is ≤1 x 10^9/μl:** Cladribine s.c. will be administered as in week 5 only, with no further drug administrations in week 53.
this schedule (Figure 1). Although the results of this experience will be reported elsewhere25,36, treatment has been well tolerated, and severe lymphopenia has generally been completely avoided.25,31 However, as induction of lymphopenia is one of the central mechanisms of action of cladribine,20 it remains to be seen whether our dose-adjustment to avoid severe lymphopenia impacts on efficacy as it has not been used in a formal clinical trial. A head-to-head trial comparing our dosing schedule with the licensed oral formulation would be the preferred design. However, since differences would likely be minor, perhaps even non-existent as similar bioequivalent doses of active compound are being used, the sample size of such a trial would be excessive and the resulting cost prohibitive. Furthermore, such a trial may not be completed before oral cladribine comes off its patent and becomes available as a generic DMT. Monitoring off-label use in the ‘real world’ would therefore be one way to establish the value of generic cladribine.23

Over and above the phase III trial evidence supporting the use of cladribine in relapsing MS with oral cladribine,19,20 trials undertaken in the 1990s with subcutaneous11,36,37 and intravenous formulations on38,39 have reported promising results in treating pwMS including those with more advanced disease.19,20 This suggests that generic cladribine could potentially supplement use of licensed oral cladribine, restricted to relapsing MS, to provide treatment for all. However, these may have different levels of efficacy and side-effects, both of which can be influenced by dose and duration of treatment.20

A short course of oral cladribine can induce disease inhibition for at least four years in most cases,20 but in common with other licensed MS treatments, there are not many long-term, real-life safety and efficacy data, which will only accumulate with use and time. However, it is anticipated that disease breakthrough will occur in some people, who may need retreatment similar to alemtuzumab therapy.20,21,28 Common concern with off-label prescription of low-cost treatments is that it may dis-incentivise drug companies from developing new treatments and investing in the care of pwMS. However, we expect these changes to occur soon anyway as the market for immunomodulatory DMT becomes increasingly crowded and patents, notably on small molecules, will expire paving the way for generic treatments. The pharmaceutical industry will need to either innovate and create more effective or safer agents or focus elsewhere. Importantly, the availability of more cost-effective immunomodulation in MS will allow companies to re-focus on unmet clinical needs, and this may remove the drug-cost barriers that can prevent other companies from developing neuroprotection and repair agents that should ideally be administered along with effective immunomodulation.

Legal aspects
In the UK, the legal implications of treating with off-label drugs are covered by the General Medical Council. Their guidance makes it clear there is no extra personal liability for doctors in relation to prescribing unlicensed medicines. As a contract between doctors and pwMS wishing to consider cladribine as a compassionate off-label DMT, we developed an information sheet, following which we obtain written informed consent. We further developed a safety checklist focusing on prior malignancies, and a screen for latent infections and common malignancies, in particular cervical neoplasia, which is completed prior to commencing treatment. Over and above routine blood tests, we recommend testing for tuberculosis, syphilis, human immunodeficiency virus-1 and -2, and hepatitis B and C. We also check baseline varicella-zoster virus serostatus and if negative we recommend vaccination. Respective documents, alongside a prescription form, can be downloaded (https://www.slideshare.net/KlausSchmierer/bartsms-informationpackcladribine) and adapted for local circumstances. Transparency towards, and safety of, pwMS are key; we therefore urge doctors to seek countriespecific guidance as applicable. We have taken a cautious approach to providing off-label therapy, such that the medical staff are familiar and comfortable with this treatment. This is the approach taken to treat MS in Western countries before licensed DMTs became available and could be used in LMIC.

In summary, whilst the importance of early effective DMT for pwMS is now well recognised,3 the cost of licensed DMT remains well above the annual income of many pwMS across the Globe. As long as this is the case, off-label treatments will remain the only option (other than: no treatment) for pwMS in LMIC. The increasing understanding that pwMS may benefit from DMT, even if they do not fulfil cost-effectiveness criteria, also underpins the use of off-label DMT in pwMS in highly regulated economies. Cladribine is a thoroughly tested selective immune reconstitution DMT with an excellent risk/benefit profile, good tolerability and high convenience that is comparable to, or often better than,
currently licensed DMTs for MS. Given its worldwide availability as a generic DMT, studies comparing cladribine head to head with local standard practises of care including, if available, licensed DMTs, should be encouraged since "generic" does not mean "substandard" treatment. Whilst we have focussed on MS, based on the deoxycytidine kinase expression profile, cladribine will function as a chemical CD19-depleting agent and as such has significant potential for use in other an even larger number of other autoimmune conditions, such as NMO or rheumatoid arthritis.27,40

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References
1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 2014; 83: 1022–1024.
2. Eskandarieh S, Heydarpour P, Minagar A, et al. Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: A systematic review. Neuroepidemiology 2016; 46: 209–221.
3. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol 2015; 15: 273–279.
4. Kohelt G, Eriksson J, Phillips G, et al. The burden of multiple sclerosis 2015: Methods of data collection, assessment and analysis of costs, quality of life and symptoms. Mult Scler 2017; 23(Suppl 2): 4–16.
5. Singhal B. Multiple sclerosis – Indian perspective. Neurol India 2015; 63: 824.
6. Gracia F and Armien B. Therapeutic armamentarium and health system coverage of multiple sclerosis in Latin America. Neuroepidemiology 2012; 38: 217–218.
7. Massacesi L, Tramacere I, Amoroso S, et al. Azathioprine versus beta interferons for relapsing–remitting multiple sclerosis: A multicentre randomized non-inferiority trial. PLoS One 2014; 9: e11337.
8. La Mantia L, Milanese C, Mascoli N, et al. Cyclophosphamide for multiple sclerosis. Cochrane Database Syst Rev 2007; CD002819.
9. Olyaeemanesh A, Rahmani M, Goudarzi R, et al. Safety and effectiveness assessment of intravenous immunoglobulin in the treatment of relapsing–remitting multiple sclerosis: A meta-analysis. Med J Islam Repub Iran 2016; 30: 336.
10. Filipini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: A network meta-analysis. Cochrane Database Syst Rev 2013; CD008933.
11. Gwathmey K, Balogun RA and Burns T. Neurologic indications for therapeutic plasma exchange: 2011 update. J Clin Apher 2012; 27: 138–145.
12. Xiao Y, Huang J, Luo H, et al. Methylprednisolone methylprednisolone for relapsing–remitting multiple sclerosis. Cochrane Database Syst Rev 2014; CD010242.
13. Spelman T, Frisell T, Piehl F, et al. Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing–remitting MS from the
Swedish MS registry. *Mult Scler.* Epub ahead of print 1 June 2017. DOI: 10.1177/1352458517713668.

14. Martinelli Boneschi F, Vaccia L, Rovaris M, et al. Mitoxantrone for multiple sclerosis. *Cochrane Database Syst Rev* 2013; CD002127.

15. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology* 2017; 88: 2115–2122.

16. Cotte S, von Ahsen N, Kruse N, et al. ABC-transporter gene-polymorphisms are potential pharmacogenetic markers for mitoxantrone response in multiple sclerosis. *Brain* 2009; 132: 2517–2530.

17. Chan A and Lo-Coco F. Mitoxantrone-related acute leukemia in MS: An open or closed book? *Neurology* 2013; 80: 1529–1533.

18. Fogarty E, Schmitz S, Tubridy N, et al. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord* 2016; 9: 23–30.

19. Comi G, Hartung HP, Kurukulasuriya NC, et al. Cladribine tablets for the treatment of relapsing–remitting multiple sclerosis. *Expert Opin Pharmacother* 2013; 14: 123–136.

20. Giovannoni G. Cladribine to treat relapsing forms of multiple sclerosis. *Neurotherapeutics* 2017; 14: 123–136.

21. Rotstein DL, Healy BC, Malik MT, et al. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 2015; 72: 152–158.

22. Siddiqui MK, Khurana IS, Budhia, S et al. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis. *Curr Med Res Opin* 2017; 28: 1–11.

23. Kalincik T, Jokubaitis V, Spelman T, et al. Cladribine versus fingolimod, natalizumab and interferon β for multiple sclerosis. *Mult Scler.* Epub ahead of print 1 August 2017. DOI: 10.1177/1352458517728812.

24. Baker D, Herrod SS, Álvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may affect MS via B-cell depletion. *Neurrol Neuroimmunol Neuroinflamm* 2017; 4: e360.

25. Ceronie B, Jacobs BM, Baker D, et al. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. *J Neurol* 2018; 265: 1199–1209.

26. Baker D, Marta M, Pryce G, et al. Memory B cells are major targets for effective immunotherapy in relapsing–multiple sclerosis. *EBioMedicine* 2017; 16: 41–50.

27. Franks SE, Getahun A, Hogarth PM, et al. Targeting B cells in treatment of autoimmunity. *Curr Opin Immunol* 2016; 43: 39–45.