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Specific aspects of immunotherapy for multiple sclerosis in Switzerland: A structured commentary

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Abstract

More than a dozen substances are meanwhile available for the disease-modifying immunotherapy of multiple sclerosis (MS). However, for some substances, there is a clear difference between approval in Switzerland (Swissmedic) and neighboring countries (European Medicines Agency (EMA)). In addition, limitations imposed by the Swiss Federal Office of Public Health in the specialties list (SL) have significant effects on use in daily clinical practice. In the following, we present consensus recommendations, which were reviewed and agreed upon by the Scientific Advisory Board of the Swiss Multiple Sclerosis Society and the Swiss Neurological Society. We explicitly focus on practice-relevant differences in the approval of MS immunotherapies in Switzerland compared with the EMA area and discuss further limitations (SL) and their impact on the use in clinical practice. Immunotherapies with the same approval in Switzerland and the EMA area and symptomatic therapies are not discussed here.

Keywords

Immunotherapy, multiple sclerosis, alemtuzumab (Lemtrada®), cladribine (Mavenclad®), daclizumab (Zinbryta®), fingolimod (Gilenya®), ocrelizumab (Ocrevus®), autologous haematopoietic stem cell transplantation

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Introduction

There is hardly any field of neurology where therapeutic progress has been so clearly tangible as the immunotherapy of multiple sclerosis (MS). More than a dozen substances with different mechanisms of action, modes of administration, target groups, and benefit-risk profiles have now been approved for relapsing forms of MS. Additionally and for the first time, a drug that alters the disease course is available for primary progressive MS, which could not be treated with immunotherapy until recently. However, the approval of individual substances can vary widely in different countries. This is particularly important for Switzerland due to various considerable differences in approval (e.g. first-line vs. second-line treatment) in directly neighboring countries (EMA approval area). In addition, there are different safety requirements for some substances. Furthermore, independently of the benefit-risk assessment as part of approval in Switzerland, there is a procedurally and institutionally separate cost-benefit assessment by the Swiss Federal Office of Public Health (FOPH) that is reflected in the specialties list (SL). The SL lists the medications reimbursed by the compulsory health insurance as well as potential limitations. The specific regulatory conditions in Switzerland lead to partly different usage in routine clinical practice that is not reflected in European or other national guidelines to date. This structured commentary aims to discuss immunotherapeutic drugs for which particular approval, safety requirements, or limitations in the SL exist in Switzerland. For this, specific features of the definitions (e.g. regarding disease activity) are considered and potential differences with the clinical study data discussed. The commentary focuses on patient selection and safety considerations that underlie approval or respective restrictions in Switzerland. If relevant, also aspects of reimbursement are discussed. The following substances are reviewed (in alphabetical order, substance/trade name®): alemtuzumab (Lemtrada®), cladribine (Mavenclad®), daclizumab (Zinbryta®), fingolimod (Gilenya®), and ocrelizumab (Ocrevus®). For methodological reasons, substances that have been approved in the EMA area but not yet in Switzerland (cladribine, Mavenclad®) or that have been withdrawn from the market but previously had partly different usage in Switzerland compared to the EMA area (daclizumab, Zinbryta®) are also included. As autologous hematopoietic stem cell transplantation (aHSCT) was approved for reimbursement with limitations in Switzerland in July 2018 but is handled differently in most countries within the EMA approval area, we have also included a short section on aHSCT.

For the remaining substances that are used in the same way as in the EMA approval area, we refer to respective current guidelines.[1] Similarly, also symptomatic treatment and acute treatment of MS relapses are not discussed here.

Methods

The group of authors comprises members from French-, German-, and Italian-speaking parts of Switzerland. Neurologists from centers focusing on the treatment of MS were invited to participate in the development of the manuscript. The neurologists were from university and non-university centers as well as from the outpatient sector. All members of the Scientific Advisory Board of the Swiss MS Society (SMSS) were also invited to participate in drafting the document. Under the coordination of the corresponding author (AC), at least two authors wrote a commentary on a substance in their respective mother language. In addition to the cited literature, the commentary was based on the current Swiss information for health-care professionals (Swissmedic), the summary of product characteristics (SmPC, EMA), and the FOPH's SL. No systematic literature review was performed. All the commentaries were integrated and then revised by other members of the author group who had not been involved in the initial drafting. In a consensus, all authors approved the revised version; however, formal criteria were not employed (e.g. DELPHI method). The methodology therefore involved structured commentaries by the authors but without following formal requirements of a guideline process.

The manuscript was then submitted to the Scientific Advisory Board of the Swiss MS Society and the Swiss Neurological Society (SNS) for further comments. The final version was then translated into French, German, Italian, and English.

We focused on aspects that are different for health-care professionals in Switzerland compared to the EMA area or that the authors consider particularly relevant for Switzerland in terms of the indication, specific safety aspects or formal requirements. The commentaries for the individual substances are structured as follows:

- substance/trade name;
- comparative table of indication according to Swiss information for health-care professionals, the SL published by the Swiss FOPH and the indication according to the EMA (SmPC); as no English version exists of the Swiss information for health-care professionals and the SL, authors translated the relevant sections from German into English;
- considerations on patient selection;
- considerations on safety aspects; and
- considerations on confirmation of cost coverage/reimbursement (if applicable).

Due to the withdrawal from the market of daclizumab and current lack of approval for cladribine tablets in Switzerland, this structure was not used for these substances. Both the Swiss Multiple Sclerosis Society and the Swiss Neurological Society supported the preparation of this

commentary through translation and other administrative work. Potential conflicts of interest for each individual author were controlled by the Ombuds Committee of the Swiss Multiple Sclerosis Society.

Commentary on individual substances

Alemtuzumab (Lemtrada®)

Indication according to Swiss information for health-care professionals (translation from the Swiss Fachinformation[2])	Indication according to the Swiss SL (translation from the Swiss SL[3])	Indication according to the SmPC (EMA)[4]
Lemtrada is used in adults with active, relapsing-remitting multiple sclerosis, defined by at least two clinical relapse events within the 2 years preceding the start of treatment, of which at least one relapse in the year before the start of treatment.	As monotherapy for active relapsing remitting multiple sclerosis (RRMS) despite treatment with at least one basic therapeutic agent or in previously untreated patients with a primary highly active form after prior confirmation of cost coverage by the independent medical examiner. Dosage: five infusions in the first year and three infusions in the second year. Treatment by specialist neurologist (FMH) with timely access to magnetic resonance imaging (MRI).	Lemtrada is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Commentary

Considerations on patient selection: RRMS. The definition of disease activity in the Swiss information for health-care professionals is completely clinical, based on relapses, regardless of any previous treatment. In addition, there is a limitation in the SL, whereby alemtuzumab should be used for previously untreated patients with a primary highly active disease course, without further definition. The SL also mentions treatment failure under prior immunotherapy as a further possibility for using the treatment, without giving details such as the time interval or type of previous therapy. In contrast to the Swiss approval, EMA has a relatively open indication for active RRMS that is not further defined. In addition, in the EMA area, imaging and clinical parameters can be used for the assessment of disease activity.

The above-mentioned criteria partly correlate with the inclusion criteria of the pivotal studies. One study (CARE MS I) included patients without prior immunotherapy who had experienced at least two relapses in the preceding 2 years and at least one relapse in the previous year (corresponding to the approval by Swissmedic).[5] A separate study (CARE MS II) included patients with prior immunotherapy who had suffered from at least two relapses in the preceding 2 years, including at least one relapse in the previous year, of which at least one relapse while on interferon-β or glatiramer acetate therapy after at least 6 months of treatment.[6] These criteria are partly reflected in the SL, which does not, however, specify the prior therapy. This mirrors clinical practice, so that in our opinion treatment failure should not be limited to prior therapy with interferon-β or glatiramer acetate but should also apply to other approved immunotherapies for MS.

As regards to the definition of disease activity according to Swiss information for health-care professionals, it should be noted that aspects such as the severity of the relapse are not considered. On the other hand, the more open definition of disease activity in the EMA area places higher demands on the prescribing doctor in terms of the individual benefit-risk evaluation.

Considerations on safety aspects

For general safety considerations, we refer to the information for health-care professionals. Among other aspects, the information for health-care professionals stipulates that treatment must be started and monitored by a neurologist experienced in the treatment of MS patients. Under alemtuzumab, even several months after the transition from natalizumab (Tysabri®) ("carry over") progressive multifocal leukoencephalopathy (PML) is possible. To reduce this risk, we recommend magnetic resonance imaging (MRI) of the brain (cranial MRI, including contrast agent and diffusion weighted imaging) close to the start of treatment with alemtuzumab. The evaluation should preferably be carried out by a (neuro-) radiologist experienced in the diagnosis of inflammatory diseases of the central nervous system. For patients with a high risk of developing PML (positive serum anti-JCV antibodies, treatment duration with natalizumab $\geq$2 years; or previous immunosuppression), it is also recommended to carry out a cranial MRI after start of the treatment. Additionally for this patient group, a lumbar puncture to determine JC virus DNA, preferably in a high sensitivity assay, is advisable prior to treatment start. Because fingolimod can also increase the

risk of PML (see below), we recommend to perform a cranial MRI during the switch from fingolimod to alemtuzumab, as described above. Some centers similarly perform lumbar puncture when switching from fingolimod to alemtuzumab, but there is no consensus regarding this approach among Swiss centers.

Overall, the approach described to reduce the risk of developing PML as part of a treatment switch is not evidence based but follows previous experience and considers the pathophysiological development of PML.[7]

Because of single cases of listeriosis and listeria meningitis under treatment with alemtuzumab, no raw or undercooked meat, soft cheese, and unpasteurized dairy products should be consumed for 4 weeks after the last infusion, according to Swiss information for health-care professionals. The SmPC in the EMA area recommends avoiding consumption of the above-mentioned foods as early as 2 weeks before the start, during and for at least 1 month after alemtuzumab infusion therapy. We support this recommendation because of the incubation time of listeriosis. The combination of sulfamethoxazol and trimethoprim can be considered for 1 month after the start of treatment.

Considerations on confirmation of cost coverage/reimbursement

According to the SL, confirmation of cost coverage is required for patients with a highly active disease form who have not received prior treatment. It is essential to note that no generally accepted definition of the term "highly active" exists and that assessment depends on the individual situation. This is therefore a judgement call, which is subject to appropriate assessment in individual cases. The treating physician makes this judgement call. Confirmation of cost coverage should not lead to a time delay with this urgent treatment for a vulnerable patient group.

Autologous hematopoietic stem cell transplantation (aHSCT)

Ordinance of the Federal Department of Home Affairs regarding benefits of the Compulsory Health Insurance (Health Insurance Benefits Ordinance, HIBO) of September 29, 1995 (as of January 1, 2019) (Translation)[8]

Hematopoietic stem cell transplantation: Procedure: Autologous hematopoietic stem cell transplantation: yes

Requirements: in evaluation—for MS at the University Hospital Zurich as part of a registry study.

Indication by interdisciplinary MS stem cell transplantation board of University Hospital Zurich. Valid from July 1, 2018 until June 30, 2024

Commentary

aHSCT is approved for scleroderma as an autoimmune disease. Within the EMA area, aHSCT is available as an approved treatment procedure for MS in few countries (e.g. Sweden) or can be used after expert opinion in some regions but is not authorized in other countries. In Switzerland, intensive immunosuppression followed by aHSCT for MS was approved for compulsory health insurance reimbursement by the Swiss FOPH on July 1, 2018, on conditions (e.g. recording of patients treated in a registry). The relevant details are currently being established and the registry is being created. Because of the available treatment alternatives, particularly for relapsing disease forms, the present lack of controlled, randomized studies of highest evidence class and the invasive nature of treatment with potentially severe side effects, this treatment is subject of controversial debate in Switzerland. The treatment should therefore currently only be used in carefully selected cases. Relevant criteria include, for example, highly active disease, low or moderate degree of disability up to EDSS 6.5, patients aged up to 50 with disease duration of not more than 10 years, and failure of previous highly active approved treatment.[9,10] Because the treatment recommendation regarding aHSCT needs to be multidisciplinary and individualized, we recommend assessment at specialized academic centers only. For details of the therapy and current evidence on the effectiveness and side effects, we refer to respective references.[9–11]

Cladribine (Mavenclad®)

Commentary

A parenteral form of cladribine is authorized in Switzerland for the treatment of hairy cell leukemia. The use of cladribine tablets to treat MS has been submitted to Swissmedic for approval in Switzerland. In the EMA area, Cladribine tablets have been approved for treating adult patients with highly active relapsing multiple sclerosis, defined by clinical or imaging findings, since August 2017.[12] The treatment is administered orally and comprises two short treatment cycles within two successive years at a cumulative dose of 3.5 mg/kg body weight.[13] The tablets are administered over a few weeks at the start of the respective treatment year. Retreatment in years 3 and 4 is not regularly scheduled.

According to the SmPC in the EMA approval area, contraindications comprise hypersensitivity to the active substance/excipients, HIV infection, active chronic infections (tuberculosis, hepatitis), initiation in immunocompromised patients, active malignant tumors, moderate-to-severe impairment of kidney function as well as pregnancy and breastfeeding.

Daclizumab beta (Zinbryta®, withdrawn from the market since March 2018)

Commentary

The monoclonal antibody daclizumab against the alpha subunit of the high-affinity IL2 receptor CD25 was approved by the EMA and Swissmedic in 2016 for treatment of adult patients with relapsing forms of multiple sclerosis. Already in the pivotal studies, there was evidence of autoimmune side effects under daclizumab therapy. The most prominent were autoimmune skin reactions with sometimes severe course. In addition, there were cases of autoimmune hepatitis (including one fatal case) and inflammatory bowel disease. After approval, further cases of these autoimmune adverse drug reactions were reported, including an additional case of fulminant hepatitis with liver failure, which proved fatal. This led to restrictions on approval in the EMA area as early as 2017, whereby daclizumab could only be used as a third-line treatment.[14]

Subsequently, further cases of meningitis and encephalitis were reported, for which the pathomechanism under daclizumab is unclear. Some of these cases were fatal. Brain biopsies showed infiltration with eosinophil granulocytes, which is not consistent with MS-typical pathology. Because of additional symptoms such as fever, generalized rashes, and eosinophilia, a "drug reaction with eosinophilia and systemic symptoms (DRESS)" involving the CNS was suspected. In addition, cases with anti-*N*-methyl-D-aspartate (NMDA) receptor antibody-mediated autoimmune encephalitis with symptoms appearing 3–4 months after discontinuing daclizumab were reported.[15] With the current state of knowledge, individual risk cannot be predicted for either autoimmune hepatitis or encephalitis. It was therefore not possible to develop an adequate risk management plan. Because of these serious side effects without any possibility of individual risk assessment, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA recommended that authorization be stopped. The manufacturer thereupon removed daclizumab from the market worldwide in March 2018.[16] After treatment with daclizumab is stopped, close clinical and monthly laboratory monitoring of these patients for at least 12 months after the last dose of daclizumab should be carried out. In case of typical symptoms (e.g. behavioral symptoms, cognitive symptoms, movement disorders, and seizures), anti-NMDA receptor antibody-mediated encephalitis should be considered, with appropriate further diagnosis and treatment carried out at a specialized center.

Fingolimod (Gilenya®)

Indication according to Swiss information for healthcare professionals (translation from the Swiss Fachinformation[17])	Indication according to the Swiss SL(translation from the Swiss SL[18])	Indication according to the SmPC (EMA)[19]
Gilenya is indicated for the treatment of patients with relapsing remitting multiple sclerosis (MS) for the reduction of relapse rate and delay of disability progression.	Treatment of relapsing remitting multiple sclerosis. Initial prescription by a specialist neurologist (FMH).	Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older: Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Commentary

Considerations on patient selection: RRMS

Phase III clinical studies have evaluated the effectiveness of fingolimod in RRMS: two trials against placebo, FREEDOMS[20] and FREEDOMS II,[21] and one study with Interferon-β-1a (30 µg im, intramuscular) as a comparator: TRANSFORMS.[22] The inclusion criteria of the three studies were similar: patients with $\geq$2 relapses in the two previous years or $\geq$1 relapse in the preceding year. The decision to use fingolimod as a first-line treatment (in Switzerland) versus second-line (EMA) is probably based on a different benefit-risk assessment of the treatment and on the interpretation of the characteristics of the patients in the studies: 57% of patients received the therapy as a first-line treatment in FREEDOMS versus 45% in TRANSFORMS.

Indication for children (<18 years) RRMS: according to the manufacturer (Novartis, communication 25. 1. 2019) fingolimod was approved by Swissmedic for paediatric patients aged 10 years and above (PARADIGMS trial).[23]

Considerations on safety aspects

For general safety considerations, we refer to the information for health-care professionals, mainly as regards heart rate monitoring for the first dosing and cardiac contraindications, ophthalmological controls (macular edema, particularly in patients with diabetes or uveitis) and the vaccination recommendations for patients with negative serological antibody testing for varicella zoster virus. Although the SL requires initial prescription by a neurologist, we deem continued regular specialist neurological monitoring essential because of rare but potentially severe side effects.

Cases of PML have recently been reported under fingolimod.[24] Nineteen cases of PML (after excluding "carry over" effects of natalizumab, Tysabri®) have been reported with an overall risk of 1/15,000 MS patients treated.[25] Eighteen of the nineteen patients suffering from PML were aged >40 and 18 of the 19 had >2 years of treatment with fingolimod. An increasing number of cases of cryptococcal infections including meningitis have been reported in the postmarketing setting.[26] Most of the cryptococcal meningitis cases were reported in patients >40 and who had received treatment for >2 years.[27] Although limited, current data suggest that the patients' age could constitute a risk factor. However, as with other studies with disease-modifying treatment, patients aged >55 were not included in the fingolimod studies. In addition, the role of immunosenescence in the context of immunosuppressive therapies has not been studied in depth.[24,25,27]

Risk stratification for PML under fingolimod has not been validated to date. As with all disease-modifying therapies, we suggest a reference brain MRI scan before starting treatment and regularly thereafter, for example, at yearly intervals. For patients with an increased PML risk, for example, after previous therapy with natalizumab (Tysabri®), more frequent MRI scans should be considered. Some centers in Switzerland perform the antibody blood test against JC virus (STRATIFYJCV™) under fingolimod and observe that anti-JCV antibodies are detected under this treatment. These centers adapt their care and monitoring depending on the results of this test (e.g. increased radiological monitoring, change of treatment) in patients > 45years old who have received treatment for >2 years.[28] There is no consensus on this approach among Swiss centers.

Ocrelizumab (Ocrevus®)

Indication according to Swiss information for health-care professionals (translation from the Swiss Fachinformation[29])	Indication according to the Swiss SL (translation from the Swiss SL[30])	Indication according to the SmPC (EMA)[31]
Ocrevus is indicated for the treatment of adult patients with active relapsing forms of multiple sclerosis (MS). Ocrevus is indicated for the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to slow down disease progression and reduce the deterioration in walking speed.	Restriction until February 29, 2020 For the treatment of adult patients with active relapsing forms of multiple sclerosis (MS). For the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to slow down disease progression and reduce the deterioration in walking speed.	Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Commentary

Considerations on patient selection: relapsing MS (RMS)

The Swiss and European approval relate to *relapsing* courses in contrast to *relapsing remitting disease courses*. The Swiss information for health-care professionals states active forms but does not further define this term. In March 2018, ocrelizumab was included in the SL for this indication without restrictions.

The European EMA approval is substantially different. The EMA's approval refers to the patient spectrum of the pivotal studies (OPERA I and II: activity defined as at least two relapses in the previous 2 years or one relapse in the preceding year; EDSS between 0 and 5.5).[32] The majority of patients investigated (>70%) were treatment naive. Although clinical relapse activity represented the key inclusion criterion in the pivotal studies, we agree that MRI imaging activity can also form the basis for treatment. However, methodological limitations concerning MRI activity in clinical practice should be critically considered. Clinical routine often does not sufficiently ensure standardization of consecutive MRI investigations (e.g. field strengths and equipment, repositioning, and protocols). This should be considered when comparing images, for example, for increase in lesion burden. In clinical practice additional, often highly individualized aspects play a role when assessing disease activity. These include, for example, duration and degree of recovery from relapses and residual functional limitations relevant for activities of daily living or occupation.

Primary progressive MS

The Swiss information for health-care professionals does not restrict usage regarding the disease duration, degree of disability, or activity on MR-imaging. Preserved ambulation is implicit in the Swiss approval, but this is not more closely defined (e.g. regarding walking aids). In addition, the general delay of disease progression is also stated in the information for health-care professionals. Accordingly, ocrelizumab has been included in the SL for PPMS since March 2018 without further restrictions. The EMA approval restricts usage in line with the pivotal study.[33] This approval study included patients aged below 55 with a disease duration of <15 years and an EDSS between 3 and 6.5. Focal inflammatory activity on imaging represents a particular feature, which is obligatory according to the EMA approval text but not according to the Swiss information for health-care professionals.

Because no immunotherapeutic alternatives exist for PPMS, the Swiss approval without further restrictions in the SL is reasonable. A delay in disease progression not only does involve patients with preserved ambulation but also preservation of other relevant residual functions can be a treatment target (e.g. arm function, fine motor skills). Detailed assessment of the disease progression in a quantitative fashion is important both before and during treatment (EDSS, multiple sclerosis functional composite with timed 25-foot walk, 9 hole peg test). Younger patients with shorter disease course and focal inflammatory activity as evidenced by imaging (gadolinium enhancing lesions on MRI) seem to particularly benefit from the treatment; however conversely, this does not mean that patients without such MRI abnormalities should automatically be excluded from this treatment.

Considerations on safety aspects

For general safety considerations, we refer to the information for health-care professionals. Among other aspects, the information for health-care professionals stipulates that treatment must be started and monitored by a neurologist experienced in the treatment of MS patients. Under ocrelizumab, "carry over" cases of PML have been reported after transition from both natalizumab and fingolimod. To reduce this risk, we recommend MRI of the brain (cranial MRI, including contrast agent and diffusion weighted imaging) close to the start of treatment with ocrelizumab. The evaluation should preferably be carried out by a (neuro-) radiologist experienced in the diagnosis of inflammatory diseases of the central nervous system. For patients with a high risk of developing PML (positive anti-JCV antibodies, treatment duration with natalizumab $\geq$2 years; or previous immunosuppression), it is also recommended that a cranial MRI be carried out after start of the treatment. Additionally for this patient group, a lumbar puncture to determine JC virus DNA, preferably in a high sensitivity assay, is advisable prior to treatment start. Some centers similarly perform lumbar puncture when switching from fingolimod to ocrelizumab, but there is no consensus regarding this approach among Swiss centers.

Attention should be paid to routine check-up for cancer (in particular regular gynecological routine check-up) and tumor aftercare. According to the Swiss information for health-care professionals, women of child bearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion; according to the SmPC issued by EMA this interval is set to 12 months.

Concluding remarks

Different benefit-risk assessments but also procedural aspects can lead to partly divergent approval.[34] Staggered submissions to the various regulatory authorities can lead to different data availability according to the time of submission. This is important because not only the relevant scientific data but also further aspects, for example, data quality and product quality, are taken into account. Cultural, political, legal, and country-specific priorities probably also play a role.[34] Other countries (e.g. emerging/developing countries) also refer to the Swiss approval. To increase the transparency of the approval process, respective reports (Swiss Public Assessment Report, SwissPAR) will be published as part of the revision of the Therapeutic Products Act (TPA, Art. 67) from 2019.

Author's Note

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