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Practice guidelines

Infections and multiple sclerosis: Recommendations from the French Multiple Sclerosis Society

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INFO ARTICLE

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ABSTRACT

Introduction. – Viral, bacterial, or fungal infections are suspected of triggering multiple sclerosis (MS) and promoting relapses of the disease and are likely to be promoted by immune-active treatments. This raises questions about the infectious workup and preventive treatment of these infections prior to their initiation.
Objectives. – To establish recommendations on infections and MS. Provide information to patients and healthcare professionals on the minimal infectious workup to be performed in an MS patient at diagnosis and prior to initiation of immuno-active therapy in MS.
Methods. – The recommendation attempts to answer four main questions about infections and MS. The French Group for Recommendations in Multiple Sclerosis (France4MS) did a systematic review of articles from PubMed and universities databases (from January 1975 to June 2020), using the RAND/UCLA formalized consensus method. The RAND/UCLA method has been developed to synthesize the scientific literature and expert opinions on health care topics and was used for reaching a formal agreement. Twenty-three experts contributed to the detailed review and a group of 63 multidisciplinary health professionals validated the final version of 36 recommendations.
Results. – It is recommended that MS patients undergo a minimal infectious workup, check their vaccination status at diagnosis, and repeat it during follow-up and before starting

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immunotherapy. Screening and preventive treatment of viral (group Herpes virus, HPV, JCV, HCV, HBV), bacterial (mycobacteria) and fungal (Cryptococcus) infections is recommended prior to the initiation of certain immuno-active MS therapies.

Discussion and conclusions. – At diagnosis of MS and prior to the choice of therapeutic strategy, it is recommended to update the vaccination schedule of MS patients in reference to the HCSP vaccination schedule and the SFSEP recommendations. Before starting immunosuppressive treatment, it is recommended to inform patients of the risks of infections and to look for a constitutive or acquired immune deficiency. Health professionals and patients should be informed of the updated recommendations on infections and MS.

1. Introduction

Infection has been suspected for a long time to trigger multiple sclerosis (MS) and to favour relapse of the disease. Sustained preventive treatments for relapse and/or progression of invalidation act in different ways but they all modulate and interfere with the immune response of the patient. So these immune-active treatments are likely to favour the emergence of viral, bacterial or fungal infections. Therefore, questions can be raised concerning the minimal common infectious profile of all the immuno-active treatments and the specific profile of each treatment, as well as the preventive treatment required for administration before emergence of infection.

2. Objectives

The aim of these recommendations on infection and MS is to provide the different participants of the health system (professionals, patients and users, decision makers) with a rigorous analysis of the state of the art concerning an accountable discussion of the infections that arise during flair-up or worsening of the handicap. It also provides a synthesis of the data of the science destined to:

- help make decisions into the choice of care;
- standardize practices;
- provide informative documents to patients and health professionals;
- give a minimal common profile of infection for all immuno-active treatments and specific profiles for each MS patient prior to initiation.

These recommendations also deal with administration of treatments for prevention of infection before the initiation of immuno-active treatment.

3. Methods

The methodology used is adapted from the recommendations of the « Haute Autorité de Santé » and a method derived from RAND/UCLA (Haute Autorité de Santé, 2007). The steering committee defined the theme of the work *infections and multiple sclerosis*. Four concrete and specific clinical questions were raised:

- What is the influence of infections on MS and the influence of MS on infections?
- Do immuno-active treatments for MS favour viral, bacterial or fungal infections?
- Which evaluations for infection should be done before immuno-active treatment for MS?
- Which preventive treatments of infections should be provided before an immuno-active treatment for MS?

The objective of these recommendations is to reply to these four clinical questions.

The documentary research was done by a group of readers using Internet websites that brought together mainly publications on recommendations and consensus. Research with the Medline data base was then performed (http://www.ncbi.nlm.nih.gov/pubmed).

An initial selection was made using keywords in English: multiple sclerosis, central nervous system demyelination, infections, herpes virus, VZV, papilloma virus, hepatitis, HIV, relapse, EBV, CMV, SARS CoV-2, enterovirus, pneumocoque, tuberculosis, cryptococcus, disability, immunomodulators, immunosuppressants, interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, cladribine, ocrelizumab, rituximab, mitoxantrone.

The groups of readers subsequently performed a systematic analysis of the literature with tests and checklists giving arguments referring to the appropriate references. Re-reading and grading was performed by all the members of the working group during virtual meetings and the written version elaborated by the coordinator reflected the many readings/re-readings of the working groups.

Each proposition for the recommendations was submitted one by one to a group of co-authors who did not participate in the initial writing during the face-to-face meetings and a virtual meeting (during the COVID-19 pandemic). Each co-author attributed a score of agreement to each proposition between 1 (total disagreement) and 9 (total agreement). To obtain an optimal consensus concerning the form and content of each recommendation went through three cycles of writing, scoring and revision. The proposed recommendation was classified into grade A, B or C according to the following

method (https://www.hassante.fr/portail/..06/etat_des_lieux_niveau_preuve_gradation.pdf):

A grade A recommendation is based on scientific proof provided by studies with a high level of proof: for example, randomized controlled trials of the highest quality and without major bias, meta-analyses of randomized controlled trials. Strong scientific evidence systematically results in a grade A recommendation irrespective of the agreement between experts. A grade B recommendation is based on scientific presumption provided by studies giving an intermediate level of proof: for example, randomized controlled trials of low power, well-conducted non randomized controlled studies, studies of cohorts. A grade C recommendation is based on studies providing a lower level of proof: for example case control studies, series of cases. In the absence of precise data the proposed recommendations reflect the opinion of the experts. In the absence of a high level of proof and agreement between experts, alternatives will be presented without making a recommendation in favour of one or the other. All the participants collaborated in the writing/re-writing at least three times by electronic email and during face-to-face meetings concerning the literature and writing (Annexe 1).

4. Question 1: What is the influence of infections on MS and the influence of MS on infections?

4.1. *1a: Are infections associated with an increased risk of developing MS?*

Recommendation 1a.:

- A history of infectious mononucleosis and of positivity to anti-EBV (anti-VCA and anti-EBNA) antibodies is associated with an increased risk of developing MS (Grade C).
- No bacterial or fungal infection has been described to be associated with an increased risk of developing MS (opinion of experts).

Strong Agreement (median 9, min-max 8–9)

Several meta-analyses and controlled case studies have shown an association between Epstein-Barr virus (EBV) infections and the risk of developing MS [1,2,3] in particular in the case of infectious mononucleosis (IMN) [4]. Positive serology to anti-EBV (anti-EBNA and anti-VCA) in adults [1,2] is associated with a risk of developing MS. Negative serology to EBV is a protective factor for the risk of developing MS [5]. Infection with varicella zoster virus (VZV) is not associated with an increased risk emergence of MS [6].

Bacterial or fungal infections are not associated with an increased risk of developing MS. Insufficient data is available to significantly link an association between Chlamydia pneumonia and an increased risk in the emergence of MS. In fact, the meta-analysis by Bagos et al. [7] revealed a large variability in the results depending on the study. However, most of them reported an increase in the presence of Chlamydia pneumoniae in the cerebro-spinal fluid (CSF) of patients with MS (detection of DNA by PCR or intrathecal synthesis of Ig anti-Chlamydia) but with no difference in the level of IgG-anti Chlamydia in the LCR or blood. Toxoplasmosis is not associated with an increased risk of developing MS [8]. Infections with Helicobacter pylori (HP) are less frequent than in the general population [9].

4.2. *1b: Are infections associated with an increased risk of triggering relapse?*

Recommendation 1b.:

The present state of knowledge does not allow an opinion to be made concerning the role of viral, bacterial or fungal infections in an increase in the risk of flair-up of patients with MS (expert opinion)

Strong Agreement (median 8, min-max 7–9)

4.3. *1c: Are infections associated with an increased risk of transitory or prolonged aggravation of disability?*

Recommendation 1c.:

- Infection is associated with an increased risk of the emergence of transitory aggravation of disability in patients with MS (grade C).
- The present state of knowledge does not allow an opinion to be made concerning possible association of an increased risk of emergence of prolonged aggravation of disability in patients with MS (expert opinion).

Strong Agreement (median 8, min-max 7–9)

Despite the fact that several case report studies and meta-analyses reported an increase in the risk of flair-up during the period surrounding infections [10–15] the role of infection in an increase in the risk of flair-up in MS was not endorsed due to: i) the lack of certitude concerning an increase in the neurological

disability of the patients with respect to relapse as defined by the MacDonald 2017 criteria and ii) the lack of studies concerning the MRI activity subsequent to infection. Even if an increase in the risk of flair-up following infection was not withheld, the experts agreed that there existed a temporary increase in the neurological disability of patients with MS.

An increase in the number of flair-ups of MS patients was noted during the influenza epidemic in the general population [16]. Yet only one level 2 cohort study found an increase in the risk of flair-up during the period of risk (RR = 3) for a variety of infections including flu [17]. So it was decided that no recommendation be made concerning influenza. We recall the recommendations made by the SFSEP [18] concerning seasonal influenza vaccination for patients with limited mobility or on immuno-suppressor treatment that recommend vaccination of the patient as well as their immediate entourage (cocooning).

Only one level 4 study concluded that a recent history of infection had no impact on residual inability of relapse [19].

4.4. *1d: Does MS promote infection?*

Recommendation 1d.:

- Upper respiratory tract infections occur more frequently in disabled MS patients than in the general population (expert opinion).
- MS patients are more often hospitalized for infection (grade C) and death from infection (grade B) than the general population, in particular for disabled MS patients (expert opinion).

Strong Agreement (median 8, min-max 7–9)

Several case reports and meta-analyses found a higher risk of infection, primarily respiratory, for MS patients than for the general population, in particularly for patients with a high degree of handicap [20,21]. No study has formally concluded that MS promotes infection in general. No publication reports the specific risk of transient worsening of disability in case of non-febrile urinary tract infection (UTI). However, in MS UTI recommendations of the SFSEP [22] the experts concluded that UTI were associated with a higher risk of temporary disability aggravation for cases of febrile UTI because of the Uhthoff phenomenon. Nevertheless, hospitalization consequent to infection appears to be twice as frequent in MS as in the general population [23]. A prospective level 2 cohort identified infection as a factor of risk of death of MS patients [24]. Regarding COVID 19 infection, a French level 2 cohort study including 347 MS patients who contracted Sars-cov-2 reveals in this population 21% severe form of COVID 19 (i.e., warranting hospitalization) and 3.5% death which is higher than the general French population. The only independent risk factor for MS-related COVID 19 severity identified in this study was disability (EDSS $\geq$ 6 OR = 6.3; [95% CI 2.8–14.4]) [25].

5. Question 2: Do immuno-reactive treatments for MS promote viral, bacterial or fungal infections?

5.1. *2a: Interferon beta*

Recommendation 2a:

No increase in the risk of infection (viral, bacterial, fungal) has been established with interferon beta treatment (grade B).

Strong Agreement (median 9, min-max 8–9)

The three large randomized multi-centric trials that compared interferon beta with placebo for 1300 patients did not find an increased risk of infection during follow-up [26] and [27–31]. In an exposed/non-exposed observational level 3 study, no increased risk of infection was found in the treated versus non-treated groups [32]. Finally, review of sustained treatment for MS did not find an increase in the risk of infection for the population on interferon beta [33,34].

5.2. *2b: Glatiramer acetate*

Recommendation 2b:

No increase in the risk of infection (viral, bacterial, fungal) has been established for glatiramer acetate (grade B).

Strong Agreement (median 9, min-max 8–9)

A randomized study (Glatiramer acetate (GA) vs placebo) including 251 patients did not report infection among the side effects recorded [35]. Two cohorts of MS patients treated with GA including 208 [36] and 232 patients [37] did not report any

infections. Reviews into the tolerance of patients to DMT did not find a general increase in the risk of infection [33] [34,38].

5.3. 2c: *Teriflunomide*

Recommendation 2c:

- No increase in the risk of infection (viral, bacterial, fungal) has been established for teriflunomide (grade C). Nonetheless the health authorities recommend enhanced surveillance with respect to the risk of infection when on teriflunomide
- Treatment with teriflunomide exposes MS patients to a rare risk of developing a mycobacterial infection (expert opinion).

Strong Agreement (median 8, min-max 7–9)

Data on tolerance have been provided principally by pivotal studies (TOPIC, TEMSO, TOWER] [39–41] Two doses of teriflunomide (14 and 7 mg/day) were tested during two years. These three studies did not find an increase in the risk of infection compared to placebo. Global analysis of four phase 2 and 3 and extension studies did not reveal an increased risk in infection [42]. The TENERE phase 3 study including 220 relapsing-remitting MS (RR-MS) on GA followed for 48 weeks did not detect an increased risk of serious infection when treated with teriflunomide. The French Authority for Health published the opinion of the Transparency Commission of 5 October 2016 after evaluation by the Pharmacovigilance Committee for Risk Evaluation (PRAC) relative to PSUR n°C2 (period 26 February 2014 to 12 September 2014) and PSUR n°3 (period from13 September 2014 to 12 March 2015) which reported, ''subsequent to marketing authorization 24 cases of septicemia, five of which were fatal, and one life threatening case were identified. The deceased patients (4 urinary tract infections, ulcer of the decubitus 1) on multiple-drug therapy had advanced stage MS. Seventeen cases of septicemia were hospitalized. During the study comparing placebo, one patient on 14 mg of teriflunomide died with bacterial septicemia. In view of the post-commercialization data and data of clinical studies the PCRE considered that the serious infections that emerged when on teriflunomide could lead to sepsis and occasionally to a fatal issue''.

A few rare opportunistic infections [43] and one progressive multifocal leukoencephalopathy (PML) correlated with natalizumab use [44]. A few cases of tuberculosis have been reported with leflunomide, the mechanism of which is similar to teriflunomide. Consequently, experts warn against the risk of tuberculosis on teriflunomide.

5.4. 2d: *Dimethyl fumarate*

Recommendations 2d:

- In the absence of chronic lymphopenia, no increase in the risk of infection (viral, bacterial, fungal) has been reported with dimethyl fumarate (DMF) (grade C)
- Treatment with dimethyl fumarate exposes MS patients to a very rare risk of developing PML (grade C).

Strong Agreement (median 8, min-max 7–9)

The pivotal studies CONFIRM, DECIDE [45,46] did not identify an increased risk of infection among patients treated with DMF. The tolerance data were confirmed by 2 additional studies that followed the patients for a minimum of 5 years [47,48]. Thirty-four cases of opportunistic infections was reported [49]. Nine cases of PML were reported by Jordan et al. [50] giving an incidence of PML in patients treated with DMF of 0.02 for 1000 patients, which corresponds to a rare undesirable event (< 0.01%) (Box 1). The two main risk factors for PML on DMF are age over 54 years and severe prolonged lymphopenia. In fact, the majority of patients reported with PML had prolonged (> 6 months) lymphopenia with < 800/mm^3 total lymphocytes count. The FDA adverse event reporting system and the medical literature analysis retrieved 34 cases of serious opportunistic infections (OIs) with a causal association with DMF. Six OIs occurred with normal circulating absolute lymphocyte counts [49].

Box 1. Characterization of side-effects by the frequency of emergence:

- Very frequent: >10%;
- Frequent: between 1 and 10%;
- Low frequency: between 0.1% and 1%;
- Rare: between 0.01 and 0.1%;
- Very rare: <0.01%.

5.5. 2e: Fingolimod

Recommendation 2e.:

- An increase in the risk of viral infection (virus of the herpes group, HPV) has been identified on fingolimod (grade C)
- Treatment with fingolimod exposes MS patients to a very rare risk of developing PML (grade C)
- No increase in the risk of a bacterial infection has been identified on fingolimod (grade C)
- Treatment with fingolimod exposes MS patients to a very rare risk of developing a cryptococcus fungal infection (grade C).

Strong Agreement (median 8, min-max 7–9)

Pivotal (FREEDOMS I, II, TRANSFORMS) studies as well as data of studies of groups have found an increase in the risk of infection for MS patients treated with 1.25 mg/day or 0.5 mg/day fingolimod [51–53]. The extension to the FREEDOMS I and TRANSFORMS studies as well as the other cohort studies including a small number of patients also tend towards this outcome [54–58].

Nonetheless, these studies point out an increased risk of labial herpes with fingolimod. Cases of opportunistic Cryptococcus infections and some herpes infections with a neuromeningeal localization have been reported [34,59,60]. The incidence of VZV infections in pivotal trials and in post-marketing studies is estimated at 11 for 1000. The risk of VZV infection is not frequent [0.1% et 1%] [61] (Box 1).

Cases of PML with an estimated incidence of 0.05/1000 patients, which corresponds to a very rare undesirable event (frequency $< 0.01\%$) have been reported (Box 1).

There exists a very rare risk (frequency $< 0.01\%$) of HPV infection for patients on fingolimod. To date 28 cases of HPV have been reported in the literature [62–64].

5.6. 2f: Cladribine

Recommendation 2f:

- An increased risk of viral infection (herpes group of viruses) has been identified when on cladribine (grade C)
- No increase in the risk of bacterial or fungal infection has been established when on cladribine (grade C).

Strong Agreement (median 8, min-max 7–9)

The phase II ONWARD, the pivotal ORACLE et CLARITY and the CLARITY extension studies evaluated the efficacy and tolerance of cladribine and did not reveal an increased risk of infection in the group treated with cladribine compare to placebo or interferon beta [65–68]. The incidence of rash (herpes-zoster virus) was higher than with placebo [69].

5.7. 2g: Mitoxantrone

Recommendation 2g:

An increase in the risk of infection (viral, bacterial, fungal) has been identified when on mitoxantrone (grade B).
Strong Agreement (median 8, min-max 7–9)

Mitoxantrone use in oncology (lymphoma, leukemia, breast cancer) is very often (frequency $> 1/10$) (Box 1) associated with infection (including with a fatal issue) (Haute Autorité de Santé), urinary tract infection, upper respiratory infection. Mitoxantrone use at different doses (12 mg/m^2, 8 mg/m^2 et 5 mg/m^2) for treatment of MS is also associated with an increased risk of bacterial infections compared to placebo. It was noted that the EDSS of patients of older studies was between 3.5 [70] and 4.5 [71,72] which also constitutes a sub-group at risk of urinary and respiratory infections [73].

5.8. 2h: Natalizumab

Recommendation 2h:

- An increase in the risk of viral infections (virus of the herpes group) has been identified when on natalizumab (grade C)
- An increase in the risk of PML has been identified with natalizumab in the case of JCV positive serology (grade A)
- In the case of JCV positive serology, the risk of PML with natalizumab increases with a JCV index >0.9, with prolonged treatment with natalizumab or with immunosuppressive treatment prior to natalizumab (grade A)
- No increase in the risk of infection (viral, bacterial, fungal) has been identified when on natalizumab (grade C).

Strong Agreement (median 9, min-max 8–9)

The pivotal phase III AFFIRM and SENTINEL trials of 1500 patients with RR MS treated with natalizumab did not find an

increase in the risk of infection compared to either the placebo or interferon beta groups [74,75]. These results were confirmed in the ASCEND study assessing natalizumab in patients with secondary progressive MS who had an average EDSS of 6 [76].

Recent reviews confirm the absence of an increase in infection with natalizumab [34,77]. But many cases of PML occur with natalizumab [78]. The individual risk of PML varies depending on the JCV serology and the duration of treatment, which varies from 0.07/1000 if the serology is negative and 10.2/1000 if the serology is positive and the index is < 1.5 with a treatment duration of > 61 months [79]. Few cases of infection with Cryptococcus [80,81] have been reported, as well as cases of infection with the herpes group of viruses [82] and a brain abscess [83].

5.9. *2i: Anti-CD20*

Recommendation 2i:

- An increase in the risk of infection (bacterial, viral and fungal) has been established with anti-CD20 for MS patients (grade C)
- The risk of infection in a patient with MS on anti-CD20 increases for cases with hypogammaglobulinemia (grade B)
- A risk of reactivation of the hepatitis B virus has been identified with anti-CD20 (grade C).

Strong Agreement (median 9, min-max 8–9)

The pivotal phase III and II (OPERA and ORATORIO) trials including 1300 patients treated with 600 mg of ocrelizumab once a week for a minimum of 2 years reported an increase in risk of infection compared to the placebo or interferon. No opportunistic infections were reported with ocrelizumab[84–86]. However, the level of infection was particularly high in these studies, with more than 10% of patients presenting with nasopharyngeal or urinary infections or symptoms of influenza. In the two studies that examined either primary progressive (PP) or RR forms, infections were more frequent than for the placebo group, notably with weekly doses of 2 g [84,87,88]. Several observational studies into PP and RRMS patients on rituximab reported frequent infections [89] 2 had urosepsis [90], but no comparative data was given. In 2008 Baror et al., reported 61% of infections, mostly ORL, respiratory and urinary, for 26 RRMS patients treated with 2 g of rituximab 6 monthly followed for 72 weeks [91]. A pediatric cohort including 114 patients with an inflammatory central nervous system disease, two of which had MS treated with rituximab, reported 11 children (7.6%) with serious infections in an average of 30 days after initiation of treatment [92].

Anti-CD20 can reactivate latent hepatitis B virus (HBV) infections. Infection was reported for one MS patient treated with ocrelizumab [93]. A high level of reactivation of HBV was observed for patients with hemopathy treated with rituximab ranging from 27% to 80% for Ag Hbs positive patients and 3 to 25% for Ag Hbs/anti Hbc + patients [94].

Hypogammaglobulinemia induced by anti-CD20 is also a factor of risk of severe and repeated infection [95].

6. Question 3: Which tests for infection should be performed before immuno-active treatment of MS?

6.1. *3a: The minimal recommended pre-therapy test for infection*

Recommendation 3a:

- It is recommended that viral serology for HIV, HBV, HCV, VZV be performed on diagnosis of MS and repeated during follow-up (expert opinion).
- In the absence of proof of vaccination against MMR, it is recommended that serology for rubella be performed for women with MS of child bearing age (expert opinion).
- In the absence of proof of MMR vaccination, it is recommended that serology for measles be performed for MS patients (expert opinion).
- Before administration of immuno-active treatment to MS patients it is recommended that questioning and general clinical examination be performed for a history of infection, present infection, risk of infection and for evaluation of the disposition of the patient (expert opinion).
- Before administration of immunosuppressive treatment to MS patients it is recommended to look for a constitutive or acquired immune deficiency with at least: a complete blood count, protein immuno-electrophoresis, assay for immunoglobulins, HIV serology and examination for latent tuberculosis (expert opinion).

Strong Agreement (median 8, min-max 7–9)

Immuno-active treatments include interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, cladribine, anti-CD20, and mitoxantrone. Immunosuppressant treatments include teriflunomide, fingolimod, natalizumab, cladribine, anti-CD20, and mitoxantrone.

Due to the risk of developing chronic lymphopenia when on dimethyl fumarate, it is advisable to not only follow the recommendations for treatment with immuno-active agents but also for immunosuppressants [18]. Immunosuppressants contraindicate live attenuated vaccines (Recommendations of the French public health council « Haut Conseil de la Santé Publique (HCSP) », article L3111-1, public health code) (Lebrun et al., 2019) (calendar for vaccinations and vaccine recommendations 2020). Attenuated live vaccines include those against measles, mumps, rubella (MMR) and vaccines against

Table 1 – Summary of the minimal testing.

Recommended test	When to perform
HIV Serology	On diagnosis and during follow-up Before immunosuppressor treatment
HBV Serology	On diagnosis and during follow-up
HCV Serology	On diagnosis and during follow-up
VZV Serology	On diagnosis and during follow-up
Rubella Serology	Women of child bearing age in the absence of proof of vaccination
Measles serology	On diagnosis in the absence of proof of vaccination
Examination for previous or present infections (questioning, clinical examination)	Before immuno-active treatment
Total blood cell count	Before immunosuppressive treatment
Immunoelectrophoresis of proteins	Before immunosuppressive treatment
Immunoglobuline assay	Before immunosuppressive treatment
Latent tuberculosis	Before immunosuppressive treatment

yellow fever virus, dengue virus, rotavirus, varicella, herpes zoster, as well as the oral vaccine against poliomyelitis and BCG. Due to the increase in the number of immunosuppressive treatments for MS the experts recommend serological testing for rubella and measles when MS is diagnosed. In fact, rubella is often a benign viral infection but when the patient is pregnant, it can lead to fetal mortality, and measles to congenital malformation. In recent years, France has experienced an epidemic flair-up of measles leading to several deaths. Measles is still a public health concern. As a result of more than 30 years of a lack of generalization of MMR vaccination, a major epidemic of measles occurred between 2008 and 2012 in France, where half of the cases concerned young adults. Thus, as of 2011 vaccination with two doses of the MMR vaccine is recommended for persons over one year and born since 1980 [96] (Table 1).

6.2. *3b: Interferon beta*

Recommendation 3b:

> In addition to minimal testing for infection before therapy, specific testing for infection is not recommended before treatment with interferon beta (grade C)
> Strong Agreement (median 9, min-max 8–9)

6.3. *3c: Glatiramer acetate*

Recommendation 3c:

> In addition to the minimal testing for infections prior to therapy, it is recommended to not perform specific testing for infection before administration of treatment with glatiramer acetate (grade C)
> Strong Agreement (median 9, min-max 8–9)

6.4. *3d: Teriflunomide*

Recommendation 3d:

> In addition to the minimal testing for infections prior to therapy, it is recommended to not perform specific testing for infection before administration of teriflunomide (grade C)
>
> Strong Agreement (median 9, min-max 8–9)

3e: Dimethyl fumarate

Recommendation 3e:

> In addition to the minimal testing for infections prior to therapy, it is recommended to not perform specific testing for infection (including JCV serology) before administration of dimethyl fumarate (grade C)
>
> Strong Agreement (median 8, min-max 7–9)

Due to the risk of developing chronic lymphopenia on dimethyl fumarate, the recommendations concerning immunosuppressants should be applied.

Nine cases of PML on dimethyl fumarate were reported by Jordan et al. (Jordan et al., 2020), giving an incidence for PML for MS patients on dimethyl fumarate of 0.02 per1000 patients, which is evaluated as a very rare undesirable event (< 0.01%) (Box 1). In so far as there are no data concerning confirmation of the accuracy and validity of the JCV index on dimethyl fumarate the experts do not recommend systematically performing JCV serology during follow-up with this treatment.

6.5. 3 f: Fingolimod

Recommendation 3f.:

- In addition to the minimal testing for infections prior to therapy, it is recommended to perform serology for VZV before giving treatment with fingolimod (grade C)
- It is recommended to systematically look for a HPV infection before administrating treatment with fingolimod (grade C)
- It is recommended to not systematically perform serology for JCV before administrating treatment with fingolimod (grade C)

Strong agreement (median 8, min-max 7–9)

The incidence of infection with VZV reported in pivotal trials and in post marketing studies is 11 per 1000, which corresponds to a low level of risk [0.1% et 1%], the experts and health authorities (ANSM) recommend performing VZV serology before administration of treatment with fingolimod [61].

Twenty-seven cases of HPV infection have been reported to date in the literature for patients on fingolimod [63,64,97]. This result calls for vigilance, the experts recommend looking for a HPV infection before giving treatment. Cases of PML have been reported with an incidence evaluated at 0.05 per 1000 patients, which corresponds to very rare side-effect (frequency $< 0.01\%$) (Box 1). The experts do not recommend performing systematically JCV serology before treatment with fingolimod [55].

6.6. 3g: Cladribine

Recommendation 3g.:

- In addition to the minimal testing for infection prior to therapy, it is recommended to perform serology for VZV before administrating treatment with cladribine (grade C)
- It is recommended to not systematically perform JCV serology before administrating treatment with cladribine. (grade C)

Strong Agreement (median 8, min-max 7–9)

Infections with herpes zoster virus are not frequent [0.1 et 1%] on cladribine but more frequent that placebo [69].

6.7. 3h: Natalizumab

Recommendation 3h.:

In addition to minimal testing for infection prior to therapy, it is recommended to perform JCV serology with measurement of the index before administration of treatment with natalizumab (grade C)

Strong Agreement (median 9, min-max 8–9)

The experts recommend performing JC virus serology with measurement of the index before natalizumab treatment. A French cohort obtained from data in the French OFSEP database found that the incidence of PML on natalizumab has decreased since 2007 [98]. The authors put forward the hypothesis that the decrease is due to the generalization of serological testing for JCV before treatment and during follow-up, which permits risk stratification [79].

6.8. 3i: Anti-CD20

Recommendation 3i.:

- In addition to minimal testing for infection prior to therapy, it is recommended to systematically perform serology for HBV before treatment with anti-CD20 (grade C)
- It is recommended to systematically test for hypogammaglobulinemia before initiating treatment with anti-CD20 (gradeC)
- It is recommended to not systematically test for JCV before treatment with anti-CD20 (gradeC)

Strong Agreement (median 9, min-max 8–9)

Anti-CD20 can reactivate a latent HBV infection. One case has been reported for a MS patient on ocrelizumab [93]. A high level of reactivation of hepatitis B virus was observed for patients with hematological disease treated with rituximab, varying from 27 to 80% for patients positive for Hbs antigen and 3 to 25% for patients negative for the Hbs antigen and positive for anti-Hbc antibodies [94].

Hypogammaglobulinemia potentially induced by anti-CD20 is a factor of risk of severe and repeated infection [95].

Nine cases of PML on ocrelizumab have been reported in the world with 8 cases attributed to previous treatment with natalizumab or fingolimod [99], which corresponds to a very rare side-effect ($< 0.01\%$) (Box 1), the experts do not recommend performing systematically JCV serology.

6.9. 3j: Mitoxantrone

Recommendation 3J:

In addition to minimal testing for infection prior to therapy, it is recommended to not perform specific testing before initiation of treatment with mitoxantrone (grade C)

Strong Agreement (median 8, min-max 7–9)

Urinary and respiratory tract infections are the main infections found in studies [70,72,73,100]. No specific type of infection was identified. So the experts recommend performing minimal pre-therapeutic testing before giving each perfusion of mitoxantrone.

7. Question 4: Which preventive treatment for infection should be given before immuno-active treatment in MS?

7.1. 4a. Vaccinal calendar

Recommendation 4a.:

At the time of diagnosis of MS and before any discussion into the choice of the therapeutic strategy, updating of the vaccinal calendar of the patient is recommended applying the vaccinal calendar of the French Public health council « Haut Conseil de Santé Publique (HCSP) » and the recommendations of the SFSEP (grade C)

Strong Agreement (median 9, min-max 8–9)

Vaccinal recommendations of the ''Sociéte Francophone de la SEP (SFSEP)'' [18] have been regularly updated, especially concerning COVID vaccination (https://sfsep.org).

7.2. 4b: Interferons beta

Recommendation 4b:

Aside from bringing up to date the vaccinal status before providing immuno-active treatment, it is recommended to not administer systematically preventive treatment for infection before initiating treatment with interferon beta (grade C)
Strong Agreement (median 9, min-max 8–9)

7.3. 4c: Glatiramer acetate

Recommendation 4c:

Aside from bringing up to date the vaccinal status before providing immuno-active treatment, it is recommended to not administer systematically preventive treatment for infection before initiating treatment with glatiramer acetate (grade C)

Strong Agreement (médiane 9, min-max 8–9)

7.4. 4d: Teriflunomide

Recommendation 4d.:

Aside from bringing up to date the vaccinal status recommended by the « Haut Conseil de Santé Publique (HCSP) », specific for initiation of immunosuppressor treatment, it is recommended to not administer systematically preventive treatment for infection before initiating treatment with teriflunomide (grade C)

Strong Agreement (median 9, min-max 8-9)

7.5. 4e: Dimethyl fumarate

Recommendation 4e.:

Aside from bringing up to date the vaccinal status French Public health council « Haut Conseil de Santé Publique (HCSP) », it is recommended to not administer systematically preventive treatment for infection before initiating treatment with dimethyl fumarate (grade C)

Strong Agreement (median 8, min-max 7–9)

Due to the risk described in the literature of chronic lymphopenia and opportunistic infections on dimethyl fumarate, this immuno-reactive treatment can be proposed in a preventive manner and considered like treatment with an immunosuppressor.

7.6. 4f: Fingolimod

Recommendations 4f.:

Aside from bringing up to date the vaccinal status and the specific recommendations of the French Public health council « Haut Conseil de Santé Publique (HCSP) « for administration of immunosuppressive treatment, it is not recommended to systematically provide preventive treatment for infection before giving treatment with fingolimod (grade C)

Strong Agreement (median 8, min-max 7–9)

7.7. 4g: Cladribine

Recommendation 4g.:

Aside from bringing up to date the vaccinal calendar specified by the French Public health council « Haut Conseil de Santé Publique (HCSP) « for administration of immunosuppressor treatment, it is recommended to not systematically provide preventive treatment for infection before giving treatment with cladribine (grade C)

Strong Agreement (median 9, min-max 8–9)

7.8. 4h: Natalizumab

Recommendation 4h:

Aside from bringing up to date the vaccinal status before providing immuno-active treatment, it is recommended to not administer systematically preventive treatment for infection before initiating treatment with natalizumab (grade C)

Strong Agreement (median 9, min-max 8–9)

7.9. 4i: Mitoxantrone

Recommendation 4i.:

Aside from bringing up to date the vaccinal calendar specified by the French Public health council « Haut Conseil de Santé Publique (HCSP) « for administration of immunosuppressor treatment, it is not recommended to systematically provide preventive treatment for infection before giving treatment with mitoxantrone (grade C)

Strong Agreement (median 9, min-max 8–9)

7.10. 4j: Anti-CD20

Recommendation 4j.:

Before giving treatment with anti-CD20, bringing up to date the vaccinal calendar specified by the French Public health council « Haut Conseil de Santé Publique (HCSP) » for administration of immunosuppressive treatment and to vaccinated with anti-hepatitis B in the case of the absence of immunization against HBV before providing treatment with anti-CD20 (grade C)
In the case of exposure to HBV including cure from the virus, it is recommended that a gastroenterologist or expert in infection be consulted before providing treatment with anti-CD20 to adjust follow-up and discuss the possibility of a antiviral treatment (grade C)

Strong Agreement (median 9, min-max 8–9)

Anti-CD20 can reactivated a latent HBV infection. Preventive treatment reduces the rate of reactivation of HBV [94].

Disclosure of interest

Caroline Papeix had participate in conferences, advisory boards and consulting activities for thepharmaceutical industry (alphabetical order): Biogen, Medday, Merck, Novartis, Roche, Sanofy-Genzyme. She is a member of the scientific

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Annexe 1. List of participants: French group for recommendation into infections and MS

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