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REVIEW

The Place of Immune Reconstitution Therapy in the Management of Relapsing Multiple Sclerosis in France: An Expert Consensus

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ABSTRACT

The treatment strategy in relapsing multiple sclerosis (RMS) is a complex decision requiring individualization of treatment sequences to maximize clinical outcomes. Current local and international guidelines do not provide specific recommendation on the use of immune reconstitution therapy (IRT) as alternative to continuous immunosuppression in the management of RMS. The objective of the program was to provide consensus-based expert opinion on the

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optimal use of IRT in the management of RMS. A Delphi method was performed from May 2022 to July 2022. Nineteen clinical assertions were developed by a scientific committee and sent to 14 French clinical experts in MS alongside published literature. Two consecutive reproducible anonymous votes were conducted. Consensus on recommendations was achieved when more than 75% of the respondents agreed or disagreed with the clinical assertions. After the second round, consensus was achieved amongst 16 out of 19 propositions: 13 clinical assertions had a 100% consensus, 3 clinical assertions a consensus above 75% and 3 without consensus. Expert-agreed consensus is provided on topics related to the benefit of the early use of IRT from immunological and clinical perspectives, profiles of patients who may benefit most from the IRT strategy (e.g. patients with family planning, patient preference and lifestyle requirements). These French expert consensuses provide up-to-date relevant guidance on the use of IRT in clinical practice. The current program reflects status of knowledge in 2022 and should be updated in timely manner when further clinical data in IRT become available.

Keywords: Multiple sclerosis; Disease-modifying therapy; Immune reconstitution therapy

Key Summary Points

This French expert Delphi consensus provides up-to-date relevant guidance on the use of immune reconstitution therapy (IRT) in clinical practice.

Highly efficacy treatments include continuous immunosuppression and IRT.

Consensus was achieved on topics related to the benefit of the early use of IRT allowing better control of the inflammatory stage of MS, and should be avoided during the secondary progressive phase.

Consensus was achieved on the fact that IRT can delay the use of continuous immunosuppression.

Consensus was achieved on defining the profiles of patients who may benefit most from the IRT strategy such as patients with family planning, patient preference and lifestyle requirements.

INTRODUCTION

The number of disease-modifying therapies (DMTs) available for the management of relapsing multiple sclerosis (RMS) has increased markedly in recent years [1]. This development has broadened the range of options for managing RMS, especially for people with higher levels of MS disease activity. It is important to individualise the management of RMS [2], and this increased choice of DMTs has facilitated identification of the right DMT for the right patient. Conversely, the increasing number of DMTs has also added increased complexity to the design of the therapeutic regimen.

Most DMTs can be considered to be immunomodulators or immunosuppressants that must be administered continuously [3]. DMTs are usually prescribed using an escalation approach, where “first-line” or “platform” DMTs are

prescribed initially, with a switch to a high-efficacy DMT [4] in the event of unacceptable breakthrough MS disease [5]. Alternatively, the "early high efficacy" approach has gained increasing attention in recent years, where high-efficacy DMTs are used immediately [5–7]. However, MS is a lifelong condition: longer exposure to the immunosuppressive effects of a continuously applied high-efficacy DMT may bring additional risk of serious adverse safety outcomes, such as serious infections or malignancy [7].

Immune reconstitution therapy (IRT) is a form of high-efficacy treatment for RMS that involves short, pulsed courses of treatment followed, in responders, by a prolonged period without MS disease activity or the need for further treatment [3, 8]. Real-world evidence has demonstrated that a majority of patients with high MS disease activity can remain free of relapses or radiological progression for years following the IRT courses, without the need for further treatment in the absence of MS disease activity [9–17].

IRT avoids both the risks associated with continuous immunosuppression and the burden of continuous treatment. The prospect of a prolonged period free of MS disease activity and from the need for continuous treatment for MS is likely to fit well with the needs and the lifestyles of some patients. However, there are no local or international guidelines that support the application of IRT as an alternative to continuous immunosuppression for the management of RMS. Accordingly, the appropriate place for IRT within the management of RMS needs to be defined, taking into account the current evidence base relating to the administration, efficacy, tolerability, safety and monitoring of IRTs.

A group of experts in the care of RMS from France have considered this question using a formal Delphi consensus procedure, a process designed to explore the level of consensus between experts on a specific topic [18–23]. The objective was to provide consensus-based expert opinion on the optimal utilization of IRT in the management of RMS. This article reports the findings from this process.

METHODS

We used a Delphi process conducted between May and July 2022 where experts in RMS care considered 19 statements (clinical assertions, CA). The overall research question was "What is the place of IRT in the management of RMS?"

The panellists were recruited from different regions of France and selected on the basis of their clinical expertise in the management of RMS. Out of the 18 healthcare professionals invited, 14 neurologists with multiple sclerosis specialty agreed to participate. The survey/questionnaire was developed by the steering committee. Nineteen clinical assertions (short, prepared statements relating to different aspects of RMS pathology and treatment, including IRT, were drafted to address the following topics: RMS disease activity, management of RMS, key characteristics of IRT, therapeutic mechanisms potentially involved in IRT, and profiles of people with RMS who might benefit most from IRT. Experts rated their agreement with each CA as "Fully agree", "Agree", "Disagree" or "Totally disagree".

The survey/questionnaire was completed via an online platform, and responders were encouraged to provide answers in writing. The process was conducted over two rounds. The first round was conducted anonymously, and the results were presented to experts with no discussion permitted. The second survey included only the CA without full consensus on the first round. At this stage, panellists had the opportunity to discuss the CA and the final level of consensus was established.

Consensus on a CA was defined as agreement ("Fully agree" or "Agree") or disagreement ("Disagree", or "Totally disagree") of more than 75% of the respondents. "Full consensus" signifies that all experts agreed or disagreed with a given CA. "Partial consensus" refers to a situation where more than 75% of experts agreed or disagreed, as defined above. "No consensus" means that less than 75% of experts agreed or disagreed with a CA. A third-party analyst was used for data processing and analysis to avoid attribution bias.

This work is based on previously conducted studies and the clinical expertise of the authors in treating patients with RMS. No new clinical

studies were performed by the authors. No patient-specific efficacy or safety data were reported; therefore, institutional review board (IRB)/ethics approval was not required for the consensus recommendations. Any previously conducted clinical studies were all IRB-approved. All panelists were aware of the objectives of the study, gave consent to participate in the meeting via email, and verbally agreed to participate in the development and publication of the recommendations.

IMMUNE RECONSTITUTION THERAPY VS. OTHER TREATMENTS FOR RMS

The process described in this article focussed on pharmacologic IRT, which currently includes cladribine tablets and alemtuzumab (Table 1) [3, 4, 8]. We do not consider in detail the use of autologous haematopoietic stem cell therapy (aHSCT), which essentially involves harvesting the patient's haematopoietic stem cells and haematopoietic progenitor cells, ablating the immune system using chemotherapy agents, and then repopulating the immune system via an infusion of infusion of autologous haematopoietic stem cells, although a brief description of this is given in the article [24, 25]. Mitoxantrone has been used as an induction therapy [8] or as an IRT [26] in the management of RMS, but concerns over the potential for cardiomyopathy [27] with this agent limit its use in the setting of RMS. Finally, anti-CD20 agents (e.g. ocrelizumab, ofatumumab) have the mechanistic potential to act as an IRT [3, 8]. Indeed, experts in the field have called for ocrelizumab, a relatively new anti-CD20 agent, to be administered in this way following observations of continued suppression of disease activity during an 18-month period off treatment in an extension phase of a randomized trial [28]. However, the labelling for this agent stipulates administration every 6 months, which is inconsistent with the posology of IRT. Accordingly, mitoxantrone and anti-CD20 agents are not included within the classification of IRT discussed here. Finally, differences exist in the qualitative and quantitative effects of different IRTs on immune cells. For example, reconstitution of B cells following alemtuzumab or aHSCT (but not cladribine tablets) involves an overshoot beyond the baseline level which is

Table 1 Classification of disease-modifying therapies for multiple sclerosis, based on their effects on the immune system

Maintenance/escalation therapy		Immune reconstitution therapy-like action	
Immunostimulation/ immunomodulation	Continuous immunosuppression	More selective[a]	Less selective[a]
Interferons	Dimethyl fumarate	Cladribine Tablets	Alemtuzumab
Glatiramer acetate	Fingolimod/siponimod		
	Ocrelizumab[b]		
	Natalizumab		
	Teriflunomide		

[a]Refers to balance of effect on adaptive immunity and innate immunity; "more selective" implies a greater effect on the former and lesser effect on the latter. [b]And other anti-CD20 agents. Autologous haemopoiteic stem cell transfusion is not included here, but would be considered to be a non-selective IRT, as it involves ablation of the patient's entire immune system (see text for details). Adapted from reference [3] according to Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/bync/4.0/)

Table 2 MS disease activity

		Level of consensus	
		Round 1	Round 2
CA1:	There is no consensual definition that differentiates betwee active and very active forms of RMS	85.7%	100%
CA2:	Parameters related to focal inflammation are more important in early RMS	92.9%	100%

The level of consensus was defined as the percentage of experts agreeing or disagreeing with each CA (see Methods)

Table 3 Management of RMS

		Level of consensus	
		Round 1	Round 2
CA3:	Currently, 2 therapeutic strategies for the treatment of patients with RMS are considered: the strategy of therapeutic escalation and the strategy of "high efficacy from the outset" treatment.	100%	–
CA4:	In view of recent data in a majority of patients, the use of "high efficacy from the outset" treatment has shown its effectiveness in delaying the evolution towards the progressive phase in RMS	100%	–
CA5:	There is a precise definition of a high efficacy treatment	No consensus	

The level of consensus was defined as the percentage of experts agreeing or disagreeing with each CA (see Methods)

believed to be associated with increased risk of secondary autoimmunity [29].

RESULTS OF THE CONSENSUS PROCESS

Achievement of Consensus Overall

Tables 2, 3, 4, 5, 6 summarise the results from the two rounds of consensus voting. The two rounds of the survey/questionnaires were completed by the 14 experts. After the second round, consensus was reached on 16/19 CA: 13 CA had 100% consensus, 3 CA had consensus greater than 75%, and there was no consensus on the remaining 3 CA.

The three CA with no consensus involved the precise definition of a high-efficacy treatment (#5), the correlation between the mechanism of action of IRT and the clinical effect related to reducing of the progression from RMS to progressive MS (#8), and IRT as a separate therapeutic strategy, alongside escalation and “early high efficacy” (#14).

Clinical Assertions Defining the Nature of RMS (Table 2)

Partial consensus on these two CA was achieved at round 1, with full consensus following round 2 of the consensus process.

Table 4 Key characteristics of immune reconstitution therapy (IRT)

		Level of consensus	
		Round 1	Round 2
CA6:	To date, the therapeutic options used in the high efficacy therapeutic strategy from the outset are immune reconstitution treatments (IRT) and continuous immunosuppressive treatments.	100%	–
CA7:	Immune reconstitution strategy (IRT) results in transient lymphopenia followed by qualitative lymphocyte repopulation	100%	–
CA8:	The therapeutic strategy by immune reconstitution treatments (IRT) leads to a prolonged qualitative change of adaptive immunity cells delaying the evolution of the progressive secondary phase	No consensus	
CA9:	The value of the immune reconstitution strategy is to delay the progression of the disease in the absence of continuous immunosuppression	92.9%	100%
CA10:	The use of immune reconstitution therapies (IRT) would delay the need for continuous immunosuppressive treatments	85.7%	100%
CA11:	Only the immune reconstitution strategy allows patients to benefit from "therapeutic holidays"	85.7%	85.7%

The level of consensus was defined as the percentage of experts agreeing or disagreeing with each CA (see Methods)

Table 5 Optimal use of immune reconstitution therapies (IRT)

		Level of consensus	
		Round 1	Round 2
CA12:	IRT used as early as possible has an advantage for reducing inflammation in the most inflammatory phase of the disease	92.9%	92.9%
CA13:	Immune reconstitution is more qualitative when IRT is performed early in the inflammatory phase of the disease	No consensus	78.5%
CA14:	Given its mode of action, the therapeutic strategy of immune reconstitution should be considered as a third therapeutic strategy, along with therapeutic escalation and "high efficacy from the outset"	No consensus	

The level of consensus was defined as the percentage of experts agreeing or disagreeing with each CA (see Methods)

CA1: There is no consensual definition that differentiates between active and very active forms of RMS (full consensus)

An algorithm for differentiating between active and very active forms of RMS (or similar terminology) would help to identify people with RMS who need treatment with a high-efficacy DMT. For example, Gholipour et al. in 2011 used demographic and disease characteristics to identify a subset of patients with "malignant MS", who were at high risk of rapid disease progression [30]. Freedman and Rush (2016) used a similar approach to identify a subset of people with RMS who are unlikely to respond to platform DMTs, and who require early intervention with highly active therapy [31]. Menon et al. (2017) used rapid progression of disability (Expanded Disability Status Scale [EDSS] $\geq$ 6 within 5 years of MS diagnosis) to define "malignant MS" [32]. A registry study in Sweden in 2020 used relapse rates in the real-world care setting to define high disease activity [33]. An expert group from the Arabian Gulf proposed categories of "active" RMS, "highly active" RMS and "rapidly evolving severe" RMS, based on relapses, radiology findings and prognostic factors [34]. Finally, a recent (2020) Delphi consensus process considered that any people with RMS with at least two relapses in the previous year could have highly active RMS irrespective of other factors [35]. Additionally, these authors considered that highly active RMS may be indicated by a single relapse with subclinical MRI activity and poor prognostic factors in a DMT-naïve patient, or for a patient on DMT by either at least one relapse + subclinical MRI activity in the previous year or by at least one gadolinium-enhancing (Gd+) lesion or at least two new or enlarging T2 lesions in the past year [35]. Further research will be needed to achieve a global consensus on the precise definition of high disease activity in RMS.

CA2: Parameters related to focal inflammation are more important in early RMS (full consensus)

Inflammation is present within central nervous system (CNS) lesions in RMS at all stages of the disease, from diagnosis to later secondary progressive disease [36, 37]. Focal inflammation has been described as being an especially important driver of CNS lesions early in the progression of RMS, and in children with RMS, and is associated with infiltration of peripheral immune cells [38–40]. Chronic, diffuse inflammation through the CNS also contributes to the pathology of MS, with a greater role during the later stages of MS disease progression [36, 37]. Other mechanisms drive the progression of axonal loss during the evolution of MS, however, and recent data suggests that disability may progress independently of inflammatory or relapse activity, a situation that has been termed "smouldering MS" (see also CA4, below) [41].

Clinical Assertions relating to the Management of RMS (Table 3)

CA3: Currently, two therapeutic strategies for the treatment of patients with RMS are considered: the strategy of therapeutic escalation and the strategy of "early high efficacy treatment" (full consensus)

CA4: In view of recent data in a majority of patients, the use of "early high efficacy treatment" has shown its effectiveness in delaying the evolution towards the progressive phase in RMS (full consensus)

Therapy for RMS is based on consideration of clinical observations (number, severity and location of relapses and disability progression) and MRI parameters (number, type and location of lesions). Nevertheless, escalation has been the usual starting point for therapeutic intervention with DMTs, most often based on the use of interferons or glatiramer acetate, followed by DMTs acting via continuous immunosuppression if MS disease activity continues at an unacceptable level. The use of the induction or IRT approaches in France has been limited by the non-reimbursement of alemtuzumab and the low use of mitoxantrone or aHSCT.

High-efficacy DMTs tend to be indicated for use in patients with breakthrough disease activity on first-line agents or naïve patients with highly active MS (however defined, see CA1, above), often based on the patient populations enrolled in pivotal trials. Several well-designed real-world studies have demonstrated benefits associated with the "early high efficacy"

approach to the prescription of DMTs compared with the traditional efficacy approach to the management of RMS, including reduced frequency of relapses, disability (EDSS) progression, MRI progression, or conversion to progressive MS, without undue safety concerns [7, 42–45]. The ongoing DELIVER MS study (clinicaltrials.gov NCT03535298) will compare the early high efficacy and escalation approaches to RMS care in 400 patients with relatively early stage RMS (less than 5 years from diagnosis), with another 400 patients entering an observational arm [46, 47]. The primary endpoint of the study will be loss of brain volume. The observational, non-interventional, TREAT-MS study (clinicaltrials.gov NCT03500328) has enrolled the largest cohort of people with RMS receiving alemtuzumab to date, and will provide valuable information on long-term efficacy and safety [48]. The primary outcome measures in TREAT-MS are time to sustained disability and change in the overall burden of MS.

As discussed above, a newly diagnosed patient has limited opportunity to demonstrate a history of highly active MS disease activity. However, prognostic factors (such as the location of a relapse/lesion, its severity, a higher frequency of relapses or disability progression, or the use of MRI or other biomarkers) can guide the use of a high-efficacy treatment early in the course of RMS [35, 49].

CA5: There is a precise definition of a high efficacy treatment (no consensus)

Different overlapping classifications have been used to categorise the efficacy of DMTs. Several approaches have been proposed for this, including defining "high efficacy" DMTs as those which suppressed relapse rates by more than 50%, and "moderate efficacy" DMTs as those that suppressed relapse activity by 30–50% [50], among others [51]. This approach has drawbacks, including the long-term shift of the overall population of people with MS towards a lower disease activity, which might alter the classification of a DMT over time, and its implicit assumption that relapse rates will remain the principal marker of a DMT's efficacy in future (see above). Many different classifications are found in the literature. For example, the Multiple Sclerosis Therapy Consensus Group and an international expert group considered high-efficacy DMTs to include alemtuzumab, cladribine tablets, natalizumab, ocrelizumab, ofatumumab or S1P modulators [6, 52], while an expert consensus from the Middle East defined high-efficacy DMTs arbitrarily as natalizumab, fingolimod, alemtuzumab, cladribine tablets and ocrelizumab [4]. Interestingly, the guideline for the pharmacological management of MS proposed jointly by the European Committee of Treatment of Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) considers that DMTs range from the "modestly effective to the highly efficacious" without providing criteria to distinguish them [53].

The lack of consensus in the literature on this topic was reflected here. Nevertheless, for convenience, IRT, natalizumab, anti-CD20 agents and S1P inhibitors will be considered to represent "high-efficacy" treatments for the purposes of this review, in common with the most common usage of this term in the literature.

Key Characteristics of Immune Reconstitution Therapy (IRT) (Table 4)

CA6: To date, the therapeutic options used in the early high efficacy therapeutic strategy are immune reconstitution treatments (IRT) and continuous immunosuppressive treatments (full consensus)

By definition, the "early high efficacy" strategy involves immediate prescription of a high-efficacy DMT (as far as this can be defined, see above) rather than DMTs usually described as first-line or platform agents [5–7]. In practice, the candidate DMTs for this approach act via continuously prescribed immunosuppression or as IRTs [3, 54].

CA7: Immune reconstitution strategy results in transient lymphopenia followed by qualitative lymphocyte repopulation (full consensus)

Treatment with cladribine tablets results in a marked but transient reduction in B lymphocytes ($CD19^+$) that returns to baseline by about 30 weeks after the second annual short course of treatment [55]. Similarly, T lymphocytes

($CD4^+$) recovered by about 40 weeks after the second treatment course, with little effect on $CD8^+$ lymphocytes, neutrophils and platelets [55–57]. Alemtuzumab also markedly and transiently reduces $CD19^+$ B lymphocytes, with a more marked effect on $CD4^+$ cells (by up to 95%) and $CD8^+$ cells (by up to 55%) [56, 58]. Recovery of B lymphocytes after alemtuzumab is characterised by an overshoot above baseline, which is believed to explain the association of this treatment with increased risk of various autoimmune conditions [56, 59]. Alemtuzumab may also suppress components of the innate immune system to a greater extent than that seen after treatment with cladribine tablets, although the bulk of its effect is on the adaptive immune system [60]. The efficacy of cladribine tablets and alemtuzumab in suppressing MS disease activity far outlasts the depletion of immune cells seen with either of these treatments, as described above [1, 8–17], which is consistent with immune cell reconstitution.

CA8: The therapeutic strategy by immune reconstitution treatments (IRT) leads to a prolonged qualitative change of adaptive immunity cells delaying the evolution of the progressive secondary phase (no consensus)

A post hoc analysis of the CLARITY study showed that treatment with cladribine tablets vs. placebo reduced the risk of progression to a level of EDSS consistent with secondary progressive MS (SPMS) [61]. Cladribine tablets and alemtuzumab induce changes in the immune phenotype, with long-term reductions in memory B cells [57, 62]. The observations of a preferential effect of IRTs on the adaptive vs. innate immune symptoms are relevant to their overall therapeutic profile and may explain the low potential of cladribine tablets (especially) to promote secondary infections [3, 63]. Dysregulation of the innate immune system in the CNS may play a role in the development of secondary progressive MS [64], although evidence for such a mechanism in reducing the progression from a relapsing to progressive MS after treatment with cladribine tablets is lacking (hence there was no consensus for CA8).

CA9: The value of the immune reconstitution strategy is to delay the progression of the disease in the absence of continuous immunosuppression (full consensus)

CA10: The use of immune reconstitution therapies (IRTs) would delay the need for continuous immunosuppressive treatments (full consensus)

In responders to treatment, the effect of IRT on MS disease activity, as indicated by relapse rates and MRI progression, long outlasts (by years) the reductions in the numbers of B and T lymphocytes, as summarised above. Importantly, both cladribine tablets and alemtuzumab have been shown to reduce the progression of disability vs. placebo or comparators in their pivotal trials (and their extensions) and in real-world practice [65–67]. The transient effect of IRTs on the adaptive immune system, with little or no effect on the innate immune system, as described above, does not imply continuous immunosuppression. By contrast, continuous immunosuppression increases the risk of adverse safety outcomes, including infections and, for some DMTs, malignancies [68, 69].

Up to 44% of patients in the extension to the pivotal CLARITY trial with cladribine tablets achieved "no evidence of disease activity" (NEDA-3, i.e. no relapses, no confirmed disability progression, no new/enlarging T2 lesions or Gd+ lesions) for up to 6 years since the beginning of treatment [70]. About 30% of patients treated with alemtuzumab achieved NEDA over 4 years [71]. There would be no clinical need to switch patients who respond well clinically to an IRT to an alternative DMT, in the absence of safety or other issues. Accordingly, successful use of an IRT would remove the need for use of a DMT acting via continuous immunosuppression.

CA11: Only the immune reconstitution strategy allows patients to benefit from "therapeutic holidays" (partial consensus)

The term "therapeutic holiday" was intended to refer to a period without the need for regular treatment. This term caused some confusion and limited the potential for consensus, as a successful response to an IRT removes the need for further treatment but does not remove the need for medical follow-up. Treatment with IRT has the potential to remove the need for continuous treatment with a DMT for years after

the initial treatment courses, for the majority of patients who have received it in clinical studies (see above). This may support the preferences of certain patients profiles with RMS, e.g. those who do not adhere well to a therapeutic regimen, or those who are worried about long-term safety concerns with a continuous treatment.

CA that Addressed Therapeutic Mechanisms Potentially Involved in IRT (Table 5)

CA12: IRT used as early as possible has an advantage for reducing inflammation in the most inflammatory phase of the disease (partial consensus)

This discussion built on that following CA2, above, where there was full consensus on the pathological importance of inflammation early in the course of RMS. Experts considered that strong suppression of inflammation following the application of IRT may assist the development of the subsequent remission of MS disease activity and help to prevent the development of chronic inflammation. The clinical evidence base currently supports the use of IRT relatively early in the progression of RMS, as the pivotal trials of cladribine tablets and alemtuzumab enrolled patients with a diagnosis of RMS and EDSS $\leq$ 5.5 and $\leq$ 3–5, respectively [72–74]. Evidence for benefit of IRT is limited in patients with SPMS (see also CA18 and CA19, below).

Proponents of this CA cited the preferential effects of IRT on adaptive, rather than innate, immunity, so that the action of IRT in resetting the immune system would be most relevant during the early, more inflammation-driven phase of MS. The lack of full consensus here is explained by reservations arising from the lack of long-term data to confirm the mechanisms of IRT at the clinical level.

CA13: Immune reconstitution is more qualitative when IRT is performed early in the inflammatory phase of the disease (partial consensus)

The principle of IRT is that transient depletion of lymphocytes is followed by reconstitution of an immune that is qualitatively less aggressive/more tolerogenic, leading to the prolonged absence of MS disease activity for a majority of patients with a history of frequent relapse described elsewhere in this article. Such an action is consistent with restoration of self-tolerance to myelin antigens, at least in part, and is likely also to explain the rebound autoimmunity seen in some patients following treatment with alemtuzumab associated with an overshoot of B cell counts to above the normal level during reconstitution (this is not seen with cladribine tablets) [58]. The changes to the immune cell phenotype that underlie the remission of MS disease activity following the application of IRT are incompletely understood (see discussion of CA7 and CA8 for more details), and further studies are required to achieve a scientific consensus on the precise mechanism of IRT. The partial consensus achieved here reflects the need for more research.

CA14: Given its mode of action, the therapeutic strategy of immune reconstitution should be considered as a third therapeutic strategy, along with therapeutic escalation and "early high efficacy treatment" (no consensus)

There was no consensus on this CA because the expert group were divided into essentially two groups. Some participants considered that the mechanism of action of IRT is sufficiently different from continuous immunosuppressants to merit its own title. The opposing view accepted the point concerning the mechanism, but still considered cladribine tablets and alemtuzumab to reside among the group of high-efficacy DMTs.

CA that Addressed the Application of Immune Reconstitution Therapy (IRT) for Specific Patient Populations with RMS (Table 6)

CA15: The use of IRT is of particular interest for the management of RMS in patients wishing to become pregnant in the mid-term (2 years) (full consensus)

All DMTs except beta-interferons and glatiramer acetate are either contraindicated (including cladribine tablets), or subject to warnings regarding their use in pregnancy (including alemtuzumab), according to their European labelling [75]. According to their

Table 6 Immune reconstitution therapy (IRT) patients profiles

		Level of consensus	
		Round 1	Round 2
CA15:	The use of IRT is of particular interest for the management of R-MS in patients wishing to become pregnant in the middle-term (2 years)	100%	–
CA16:	The use of IRTs is of particular interest for patients whose situation makes it difficult for them to access repeated hospital care (geographical distance and/or professional activity)	92.9%	100%
CA17;	The choice of treatment should consider the patient's preferences on the different administration schemes	92.9%	100%
CA18:	The expected clinical benefit of IRT will be limited in patients during the secondary progressive phase	100%	–
CA19.	The expected clinical benefit of an IRT will be important before the secondary progressive phase.	85.7%	100%

The level of consensus was defined as the percentage of experts agreeing or disagreeing with each CA (see Methods)

European Summary of Product Characteristics, patients are advised to delay pregnancy for 6 months after completing treatment with cladribine tablets and for 4 months after completing treatment with alemtuzumab, i.e. for about 19 months and 17 months after starting treatment, respectively. Thus, there will be a window of opportunity for responders to IRT to complete a pregnancy without the need for intake of a DMT [74, 76].

CA16: The use of IRTs is of particular interest for patients whose situation makes it difficult for them to access repeated hospital care (geographical distance and/or professional activity) (full consensus)

CA17: The choice of treatment should consider the patient's preferences on the different administration schemes (full consensus)

Incorporating patient's individual needs and preferences into the shared therapeutic management plan is a core tenet of the care for person with MS, as it is for all other conditions. In this case, the administration regimens for DMTs for RMS vary from oral (cladribine tablets, S1P modulators, teriflunomide, dimethylfumarate), self-injectable (beta-interferons, GA, ofatumuab) or infusions (anti-CD20, natalizumab, alemtuzumab, mitoxantrone). Thus, there is considerable scope for incorporating discussion of administration regimens into the discussion on preferences. Oral therapies are the most convenient to administer, as long as patients adhere to the regimen [77–79]. Infusional therapies need to be administered at hospital, which is of direct relevance to CA16. Again, when considering the benefit of prescribing a convenient therapy that minimises the need for hospital visits, it is important to remember the need for rigorous follow-up.

The burden of monitoring also needs to be considered. For example, fingolimod is an oral therapy, but patients should be monitored for 6 h following a first dose (or the first dose after an interruption of therapy), due to the risk of bradycardia, according to its European label. Infusional DMTs are also subject to monitoring requirements between administrations [4]. Monitoring requirements for cladribine tablets are relatively low, and mainly concerned with ensuring that the lymphocyte count is greater than 800 mm^{-3} before initiating the second course, monitoring for infections and for lymphocyte recovery where the lymphocyte count falls to less than 500 mm^{-3}, and initiating prophylaxis for varicella zoster prophylaxis where the lymphocyte count falls to less than 200 mm^{-3} [80, 81]. A requirement for a liver

function test before initiation of cladribine tablets has been added to the European label, following reports of rare but potentially serious drug-induced liver injury following administration of this treatment. A need for further liver function testing during treatment is driven by the appearance of signs of symptoms of hepatic dysfunction.

CA18: The expected clinical benefit of IRT will be limited in patients during the secondary progressive phase (full consensus)

CA19: The expected clinical benefit of an IRT will be important before the secondary progressive phase (full consensus)

The pivotal phase III trials of cladribine tablets and alemtuzumab were conducted in populations with RMS and EDSS $\leq$ 3–5.5, as described above [72–74]. The significant reductions in relapse rates and confirmed disability progression in this trial and in its post-trial long-term extension [67] identify high-risk patients with RMS as the principal candidates for treatment with cladribine tablets. Treatment with cladribine tablets increased the average time to onset of secondary progressive MS in the CLARITY population [61], and comparable findings have been published for alemtuzumab [82]. Evidence is limited for benefit of IRT in SPMS per se. A short (1 year), small (N = 51) randomised evaluation of parenteral cladribine suggested some efficacy in secondary progressive MS (SPMS) [83], although this requires confirmation [84]. Preliminary data in 15 patients with SPMS also suggested reduced disability progression with alemtuzumab [85]. All of these patients had experienced at least one or two relapses in the previous year, and so may have met the criteria for "active secondary MS" included as an indication in the drug's US label. The consensus on these CA is therefore in line with published clinical evidence.

A NOTE ON AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)

aHSCT is used increasingly in the management of highly active RMS (and other autoimmune diseases), but was not discussed during the Deplhi process described here, as it requires specialist centres and carries a higher risk of short-term toxicity compared with other immunomodulatory approaches [25]. Nevertheless, aHSCT may be considered to be a form of IRT and will be considered briefly here. The application of aHSCT involves mobilisation of haematopoietic stem cells (HSCs) and their progenitor cells, and ablation of lymphocytes using chemotherapy including cyclophosphamide and granulocyte colony stimulating factor. HSCs are harvested and subsequently reinfused, leading to reconstitution of the immune system and (in responders) suppression of MS relapses [24, 86].

Randomised evaluations of aHSCT are lacking, and most information is from real-world analyses [87]. A recent meta-analysis (2022) showed that, compared with before treatment, aHSCT reduced the frequency of MS relapses, and MRI activity decreased disability (EDSS score), and promoted NEDA (68% of patients) [88]. Retrospective observational data suggest that aHSCT is effective in patients with insufficient response to previous IRT [89]. Further observational data suggested that aHSCT was more effective in preventing relapses than fingolimod (hazard ratio [HR] 0.55 [95% CI 0.37–0.91]), with a greater likelihood of improvement in EDSS score (HR 2.62 [95% CI 1.46–4.72]); the efficacy of aHSCT and natalizumab was broadly similar [90]. Short-term safety issues with HSCT concern suitable prophylaxis/vaccination to prevent viral reactivation, febrile neutropenia and opportunistic infections, as for pharmacologic IRT [25, 87]. Patients receiving aHSCT require counselling on the possibility of longer-term safety issues such as the potential for adverse effects on gonadal function and fertility and secondary autoimmune disease, especially in the thyroid gland [25, 91].

Current expert guidance recommends consideration of aHSCT for patients with RMS who have had in the previous year at least two clinical relapses, or one clinical relapse with Gd-enhancing lesion(s), or new T2 MRI lesions separated in time, despite the use of at least one DMT [25]. Ideally, according to this guidance, patients should be ambulatory (EDSS $\leq$ 5.5),

aged less than 45 years and with MS disease duration less than 10 years [25]. There is no doubt that the use of aHSCT is increasing among people with RMS and other autoimmune disorders and further study, including in randomised trials, will be needed to compare the efficacy and long-term safety of this treatment compared with pharmacologic IRT and other DMTs for patients with highly active RMS disease activity [92]

DISCUSSION

Pharmacologic IRT is a relatively new modality of DMT for RMS, with potential to delay MS progression in the absence of continuous immunosuppression [3, 8]. Randomised phase III trials of IRT and their extensions have demonstrated prolonged periods of remission of MS disease activity in substantial proportions of patients, as described above [14, 72–74]. The escalation approach to MS care is likely to leave patients with highly active RMS exposed unnecessarily to the risk of MS disease activity and progression. Accordingly, the "early high efficacy" approach, with initial prescription of a high-efficacy DMT, may be more effective for this population, but may leave patients at risk of serious side effects from a continuously administered treatment (e.g. CA3, CA4). The IRT approach brings the advantage of the early high efficacy approach, with potential for delaying MS disease progression without the need (or at least, postponing the need) for long-term immunosuppressive treatment (e.g. CA6, CA9, CA10). Despite the lack of long-term data to confirm the correlation between the mechanisms of IRT and clinical outcome, the expert consensus described here identified strong suppression of inflammation early in the course of MS to be a likely beneficial consequence of IRT; this in turn supports the use of IRT earlier rather than later in the course of MS (e.g. CA2, CA12, CA13, CA18, CA19).

Experts agreed on the importance of individualised care for MS, taking into account needs and preferences, as well as MS disease characteristics (CA17). IRT may be an especially useful option for patients with RMS who find it difficult to access healthcare, do not adhere well to treatment, do not want continuous treatment, or are planning a pregnancy (CA11, C15–17). The tolerability and safety of individual currently available IRTs differ considerably, which also impacts the design of the treatment regimen for RMS. The safety profile of cladribine tablets appears to be promising, with a low risk of grade 3–4 lymphopenia and little or no potential for malignancy [80, 81]. Most side effects of cladribine tablets relate to reactivation of infections such as varicella zoster, or tuberculosis (screening and appropriate treatment/vaccination minimises these issues in clinical practice) [80, 81]. The therapeutic use of alemtuzumab in RMS has been limited by cardiac issues and the development of autoimmune conditions relating to an overshoot of lymphocyte counts above the baseline value following recovery [93]. The burden of post-treatment monitoring is also lower for cladribine tablets, compared with alemtuzumab [3]. Real-world studies will be important for confirmation of the efficacy and, particularly, the safety of IRT when used in routine MS care. We also need more information on the precise immunological mechanisms of IRT (CA7, CA8) at different stages of RMS.

There was no consensus on the definition of a highly active DMT (CA5), and the MS experts here found no consensus on whether IRT constitutes a separate class of DMT that is separate from other DMT considered to be highly active in RMS (CA14). There is a lack of consensus in the literature on these issues, and also on the clinical criteria for defining different levels of MS disease activity (CA1). Consensus here would support the effective, evidence-based prescribing of the right DMT for the individual person with RMS.

The contents of this article reflect expert opinion, based on the current published evidence base for the use of IRT in patients with RMS. The structured approach used here adds strength to this consensus. A recent expert review of Delphi methodology listed "identification of problem area of research, selection of panel, anonymity of panellists, controlled feedback, iterative Delphi rounds, consensus criteria, analysis of consensus, closing criteria,

and stability of the results" as indicators of the quality of a Delphi consensus [94]. Our analysis considered a closely defined research question, limited feedback from experts in the early part of the process, employed a second round with rules defined a priori, and had closing criteria based on clear definitions of levels of consensus. Although a second-round process cannot define the statistical stability of results (the final quality indicator), our process largely met these quality requirements. Finally, the limited number of experts involved may represent a limitation, but precise outcomes are feasible with small expert panels in Delphi processes [19], and our expert panel were considered to represent a useful cross section of RMS care in France. Accordingly, we believe that the results of our process described accurately the level of consensus between these experts in MS care.

CONCLUSIONS

This French expert consensus provides up-to-date relevant guidance on the use of IRT in clinical practice. Consensus was achieved on topics related to the benefit of the early use of IRT allowing better control of the inflammatory stage of MS, and IRT should be avoided during the secondary progressive phase. This consensus described that IRT can delay the use of continuous immunosuppression and defined the profiles of patients who may benefit most from the IRT strategy such as patients with family planning, patient preference and lifestyle requirements. The current Delphi consensus reflects status of knowledge in 2022 and should be updated in timely manner when further clinical data in IRT become available.

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Compliance with Ethics Guidelines. This work is based on previously conducted studies and the clinical expertise of the authors in treating patients with RMS. No new clinical studies were performed by the authors. No patient-specific efficacy or safety data were reported; therefore, institutional review board (IRB)/ethics approval was not required for the consensus recommendations. Any previously conducted clinical studies were all IRB-approved. All panelists were aware of the objectives of the study, gave consent to participate in the meeting via email, and verbally agreed to participate in the development and publication of the recommendations.

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