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«Διεξαγωγή μίας μετα - ανάλυσης κλινικών δοκιμών για την Αλεμτουζουμάμπη στη θεραπεία της Πολλαπλής Σκλήρυνσης από το 2010 έως το 2020»

«Perform a meta - analysis of RCTs for Alemtuzumab in Multiple Sclerosis published from 2010 to 2020»

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1.1. ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η σκλήρυνση κατά πλάκας είναι μια χρόνια αυτοάνοση φλεγμονώδης νόσος. Η Αλεμτουζουμάμπη, ένα ανθρώπινο μονοκλωνικό αντίσωμα, είναι μια πολλά υποσχόμενη θεραπεία για την υποτροπιάζουσα μορφή της νόσου.

Στόχοι: Η σύγκριση της αποτελεσματικότητας και της ασφάλειας της αλεμτουζουμάμπης με την ιντερφερόνη βήτα 1α.

Μέθοδοι: Έγινε λεπτομερής αναζήτηση στις βάσεις δεδομένων Medline, Pubmed, Scopus και Google Scholar για τον εντοπισμό σχετικών κλινικών δοκιμών. Από τις τρεις μελέτες που εντοπίστηκαν, οι δύο είχαν δημοσιευθεί την περίοδο 2010 έως 2020. Το πρόγραμμα Open Meta-analyst χρησιμοποιήθηκε για την πραγματοποίηση των συγκρίσεων μεταξύ των θεραπειών.

Αποτελέσματα: Παρατηρήθηκε στατιστικά σημαντική διαφορά προς όφελος της αλεμτουζουμάμπης στον αριθμό των ασθενών που είχαν μία τουλάχιστον υποτροπή και στον αριθμό των ασθενών με επιδείνωση της αναπηρίας. Στατιστικά σημαντική διαφορά προς όφελος της ιντερφερόνης παρατηρήθηκε στον αριθμό των ασθενών με τουλάχιστον ένα ανεπιθύμητο συμβάν, αλλά όχι σημαντική διαφορά στον αριθμό των ασθενών με σοβαρό ανεπιθύμητο συμβάν. Στατιστικά σημαντική διαφορά προς όφελος της αλεμτουζουμάμπης υπολογίστηκε για τη μέση μεταβολή του EDSS σκορ, για τον αριθμό των ασθενών με νέες T2 εστίες στη μαγνητική τομογραφία και στον αριθμό των ασθενών που αναγκάστηκαν να διακόψουν τη θεραπεία λόγω ανεπιθύμητων ενεργειών.

Συμπέρασμα: Η αλεμτουζουμάμπη αποδείχθηκε πιο αποτελεσματική από την ιντερφερόνη βήτα 1α σε όρους οφέλους για τους ασθενείς με υποτροπιάζουσα-διαλείπουσα μορφή. Τα ανεπιθύμητα συμβάντα ήταν εξίσου υψηλά και για τα δύο φάρμακα.

Λέξεις κλειδιά: Πολλαπλή σκλήρυνση, Αλεμτουζουμάμπη, Αποτελεσματικότητα, Ασφάλεια

1.2 ABSTRACT

Introduction: Multiple sclerosis is a chronic autoimmune inflammatory disease. Alemtuzumab, a humanized monoclonal antibody, is a promising treatment for relapsing- remitting MS.

Goals: To compare efficacy and safety of alemtuzumab to Interferon beta 1a.

Methods: An extensive search in Medline, Pubmed, Scopus and Google Scholar was held to identify relevant clinical trials. From three studies found, two were published in the period 2010 to 2020. Open Meta-analyst was used to perform treatment comparisons.

Results: There was a significant difference in favour of alemtuzumab in the number of participants experiencing at least one relapse and in the number of participants with sustained accumulation of disability. There was a significant difference in favour of interferon in the number of participants with at least one adverse event but not a significant difference in the number of participants with at least one serious adverse event. There was a significant difference in favour of alemtuzumab in mean EDSS score change, in the number of participants with new T2-hyperintense lesions on MRI and in the number of participants who experienced treatment discontinuation caused by adverse events.

Conclusion: Alemtuzumab was proven to be more effective than IFN beta 1a. in terms of benefit for people with RRMS. The rates of adverse events were similarly high for both treatments.

Keywords: Multiple sclerosis, Alemtuzumab, Effectiveness, Safety

2. INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease which is characterized by inflammation, demyelination, and degeneration of the central nervous system (CNS). To date, the etiology of MS remains unknown; however, it likely results from a multifactorial pathway of breakdown of immune tolerance related to genetic predisposition, environmental triggers, and immune dysregulation [1]. The age of onset is typically between 20 and 40 years [2]. The overall incidence of MS is 3.6 and 2.0 cases per 100,000 person-years in women and men, respectively. It is one of the world's most common neurological disorders, and in many countries, it is the leading cause of nontraumatic neurological disability in young adults [3]. Approximately 2.3 million people are estimated to live with MS globally [4]. Women have an approximately twofold increased risk of developing MS than men do [5].

The clinical phenotypes of MS include relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and progressive-relapsing MS (PRMS). The development of progression after a relapsing-remitting course is responsible for permanent long-term disability; it supervenes in about 80% of RRMS people by 20 to 25 years from disease onset [6]

The two past decades have marked the advent of various new therapeutic strategies in multiple sclerosis [1]. Disease-modifying treatment has been rapidly evolving. Its' goal is to reduce the early clinical and subclinical disease activity that eventually contributes to long-term disability [7, 8]. Despite all available treatment options, none are curative, and none have been proven to offer neuroprotection or contribute to neural repair.

Interferon beta-1b, interferon beta-1a (Rebif), interferon beta-1a (Avonex), and glatiramer acetate were the first agents approved by national regulatory agencies. The introduction of disease-modifying therapies (DMTs) two decades ago has clearly made a significant impact on the treatment of MS [1]. According to the same authors in average, all injectable DMTs have demonstrated a beneficial effect on decreasing annual relapse rates by approximately 30% when compared with placebo. However, they are partly effective, and their long-term impact on disease progression remains unclear. Moreover, their parenteral administration and side effects often impede patient adherence.

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In the next decade several new oral disease-modifying therapies were authorized (such as FTY720 or Fingolimod, Fumaric acid, Cladribine, Teriflunomide and HMG-CoA Reductase Inhibitors). These therapies have each demonstrated significant efficacy on various markers of multiple sclerosis disease activity in large, randomized controlled trials in patients with relapsing-remitting MS [9- 14]

Among the most promising new therapies for MS are considered monoclonal antibodies (mAbs). They are a group of selective agents, which bind to specific molecules on the surface of targeted cells, for example, T cells or B cells, both of which appear integral in the pathogenesis of MS. These include natalizumab, alemtuzumab, rituximab and daclizumab [1]. However, they have several limitations, including associated severe adverse events, infusion-related reactions, and development of neutralizing antibodies [15].

The treatment landscape continues to change rapidly. This therapeutic revolution has occurred largely due to the improved understanding of the pathophysiology of MS and unquestionably has improved the prognosis and overall quality of life for patients. The increasing number of available disease-modifying treatments has made the clinical management of patients more complex [16]. Patients and providers now have multiple options and improved flexibility in managing MS [17]. Due to a paucity of head-to-head trials, comparisons between the effectiveness of DMTs are limited in the management of multiple sclerosis (MS), a wide variety of new disease-modifying therapies (DMT) have been recently introduced what brings new opportunities for individualized therapy, where patients and healthcare providers must balance considerations of efficacy, side effects and long-term impact in a shared decision process. [18]. As a result, patients' preferences become more important in decision-making [19]. Since MS is a debilitating life-long condition seriously affecting the quality of life and the clinical outcome is directly related to patient adherence to treatment [20] high patient satisfaction with the chosen DMT plays a key role in successful MS management.

2.1 Alemtuzumab

Therapeutic strategies for MS aim to treat exacerbations, prevent new ones and avoid progression of disability [21]. Current disease-modifying treatments decrease the frequency of relapse and modestly reduce the accumulation of disability [22,23]. New agents that effectively control the disease are needed.

Alemtuzumab (CAMPATH-1H) is a humanized monoclonal antibody (mAb) that binds to the CD52 antigen on the surface of thymocytes, natural-killer (NK) cells, and B cells. Binding to the CD52 antigen results in antibody-dependent lysis and rapid removal of T cells from blood, bone marrow, and organs. This T-cell depletion lasts for an extended period of time, up to 16 months [1].

In 2001, alemtuzumab was approved for fludarabine-resistant B-cell chronic lymphocytic leukaemia. Since that time, it has been used for several other diseases (licensed or off-label use), including immune thrombocytopenic purpura, aplastic anaemia, autoimmune haemolytic anaemia, vasculitis, hematopoietic stem cell transplants (as a conditioning regimen) and organ transplants (as an induction agent). Alemtuzumab is already approved for MS in the European Union (from EMA in 2013). The US Food and Drug Administration (FDA) approved alemtuzumab for the treatment of people with RRMS who have had an inadequate response to two or more drugs indicated for the treatment of MS in 2014. Alemtuzumab is available for the treatment of MS in 12 mg/1.2 mL single-dose vials (10 mg/mL). The proposed initial dosage for MS is 12 mg daily for five consecutive days (intravenous infusion), followed by a second treatment course of 12 mg/daily for three consecutive days. The second treatment course is administered 12 months after the first course.

3. METHODS

3.1 Search strategy

A literature search was conducted in September 2020 through the following databases:,Medline, Scopus and Pubmed. A combination of the following keywords were used as search terms: multiple sclerosis OR MS AND Alemtuzumab OR Lemtrada OR CAMPATH-1H. The search was supplemented through the searching of references lists of returned articles and the use of the same search terms in Google Scholar.

3.2. Study identification

The population of interest was participants of any gender and age with RRMS fulfilling McDonald diagnostic criteria, disease duration of 10 (CARE MSII) or 5 (CARE MS I) years or less; at least two attacks in the previous 2 years with at least one in the previous year(CARE MS I); at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment; expanded disability status scale (EDSS) scores 3.00 or less (CARE MS I) or 5.00 or less (CARE MS II); and cranial and spinal MRI lesions attributable to multiple sclerosis. Key exclusion criteria included progressive forms of multiple sclerosis, previous multiple sclerosis disease therapy (apart from corticosteroids), previous immunosuppressive, investigational, or monoclonal antibody therapy, and clinically significant auto immunity other than multiple sclerosis. Clinical trials were the only studies identified as appropriate for inclusion where the outcomes of alemtuzumab were compared to those of interferon beta 1a. Only articles published in English from 2010 to 2020 were considered.

3.3 Statistical analysis

Statistical analysis was conducted using the Open Meta-analyst software to determine differences in benefit and in security between alemtuzumab and interferon patients. For dichotomous variables, the difference between the groups were calculated using odds ratio (OR) and for continuous variables using mean differences (MD). Statistical significance was set on 0.05. Heterogeneity was determined using the Q-statistic. Where there was evidence of

heterogeneity (Q greater than the 10% point of the χ^2-distribution with n-1 df), the meta-analysis was performed using the random-effects model (RE) approach instead of the fixed-effects model (FE).

3.4 Estimation of bias

Both studies were at low risk of bias for random sequence generation. They were considered as randomised as they referred to an interactive voice response system through which randomization was achieved. Randomisation was stratified by site. For the same reason they were both considered as at low risk of bias for allocation concealment. Both studies were at high risk of performance bias because both drugs had adverse effects that precluded double-blinding. As well as this, interferon beta 1a proprietary syringes could not effectively be duplicated for placebo. However, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses. Both trials were at low risk of reporting bias as they reported all specified primary and secondary outcomes.

4. RESULTS

4.1. Study characteristics

CARE-MS I enrolled adults aged 18 to 50 years with previously untreated RRMS. Participants received annual intravenous cycles of alemtuzumab 12 mg per day or subcutaneous IFN beta 1a 44 μg three times per week. CARE-MS II enrolled adults aged 18 to 55 years with RRMS and at least one relapse on IFN beta or glatiramer. Participants received subcutaneous IFN beta 1a 44 μg three times per week, annual intravenous cycles of alemtuzumab 12 mg per day or annual intravenous cycles of alemtuzumab 24 mg per day. The 24 mg per day group was discontinued to aid recruitment. Data were included for safety assessments, but they were not included in benefit assesments. In total 1191 patients were included in both studies, 802 allocated to receive alemtuzumab and 389 IFN beta 1a. In safety assessments, 811 patients received alemtuzumab and 389 IFN beta 1a.

4.2 Number of participants experiencing at least one relapse at 24 months

The two trials assessed the number of participants experiencing at least one relapse at 24 months. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 0,453, there was no significant heterogeneity across studies, and we were eligible to use the FE model. There was a significant difference in favour of alemtuzumab (OR 0.46, 95% CI 0.36 to 0.59), p< 0.001).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	82/376	75/187	45.88%	0.42(0.28-0.61)
CARE MS II	147/426	104/202	54.12%	0,50(0.35-0.70)

Table 1. Comparison of number of participants experiencing at least one relapse at 24 months
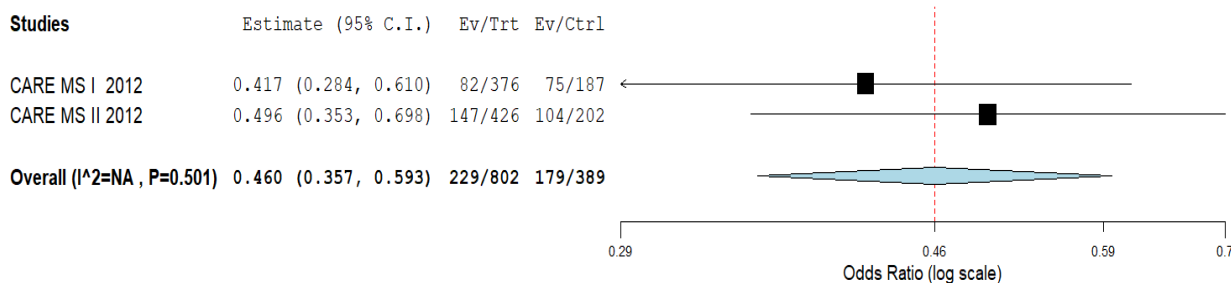

Figure 1. Forest plot of comparison of number of participants experiencing at least one relapse at 24 months

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4.3 Number of participants whose disability worsened at 24 months

The two trials assessed the number of participants with sustained accumulation of disability confirmed over 6 months. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 0,300, there was no significant heterogeneity across studies, and we were eligible to use the FE model. There was a significant difference in favour of alemtuzumab (OR 0.63, 95% CI 0.44 to 0.91), p=0.013).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	30/376	20/187	34.16%	0.72(0.40-1.31)
CARE MS II	54/426	40/202	65.84%	0.59(0.38-0.92)

Table 2. Comparison of number of participants whose disability worsened at 24 months
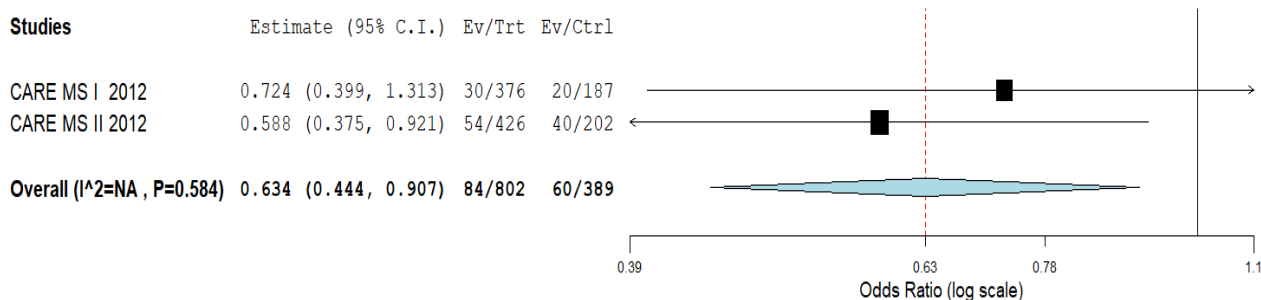

Figure 2. Forest plot of comparison of number of participants whose disability worsened at 24 months

4.4 Number of participants with at least one adverse event

The two trials assessed the number of participants with at least one adverse event. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 0,699, there was no significant heterogeneity across studies, and we were eligible to use the FE model. There was a significant difference in favour of IFN (OR 2.54, 95% CI 1.42 to 4.56), p=0.002). There was a 3 times greater risk of adverse events when treated with alemtuzumab.

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	361/376	172/187	68.59%	2.10(1.00-4.39)
CARE MS II	428/435	191/202	31.41%	3.52(1.34-9.22)

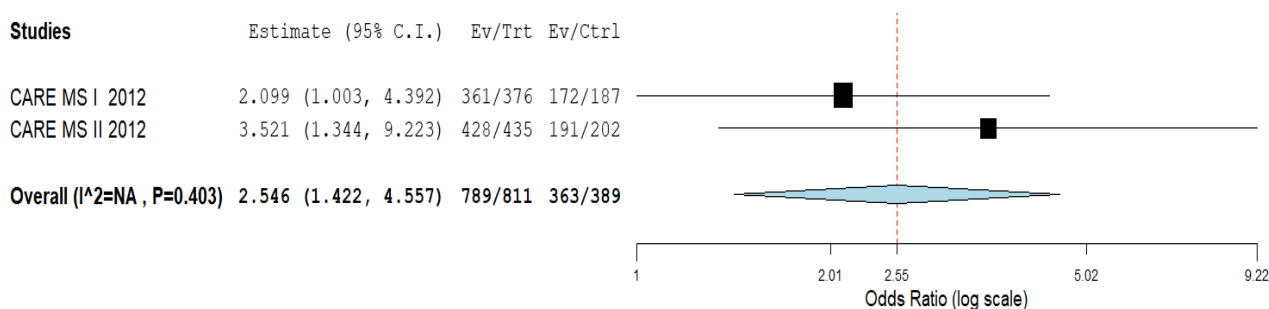**Table 3.** Comparison of number of participants with at least one adverse event

Figure 3. Forest plot of comparison of number of participants with at least one adverse event

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4.5 Number of participants with severe adverse events at 24 months

The two trials assessed the number of participants with at least one adverse event. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 1,71, there was no significant heterogeneity across studies, and we were eligible to use the FE model. There was not a significant difference in favour of any medication (OR 1.05, 95% CI 0.77 to 1.43), p=0.777).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	69/376	27/187	37.85%	1.33(0.82-2.16)
CARE MS II	85/435	44/202	62.15%	0.87(0.58-1.31)

Table 4. Comparison of number of participants with severe adverse events at 24 months
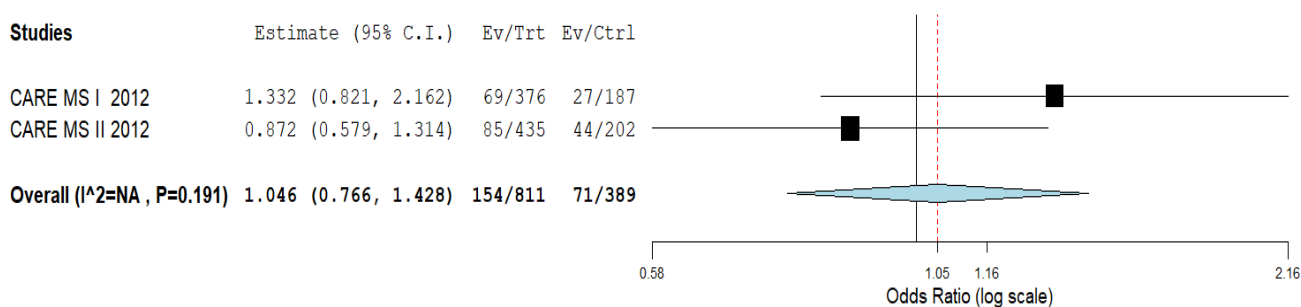

Figure 4. Forest plot of comparison of number of participants with severe adverse events at 24 months

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4.6 Mean EDSS score change from baseline at 24 months

The two trials assessed the mean EDSS score change from baseline at 24 months. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 7,604 there was significant heterogeneity across studies, so the RE model should be used. There was a significant difference in favour of alemtuzumab in disability worsening (MD 0.20, 95% CI -0.59 to 0.20).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	MD
CARE MS I	-0.1(1.1)	-0.1(1)	50.86%	0.00(-0.19-0.19)
CARE MS II	-0.2(1.3)	0.2(1.2)	49.14%	-0.40(-0.61- 0.19)

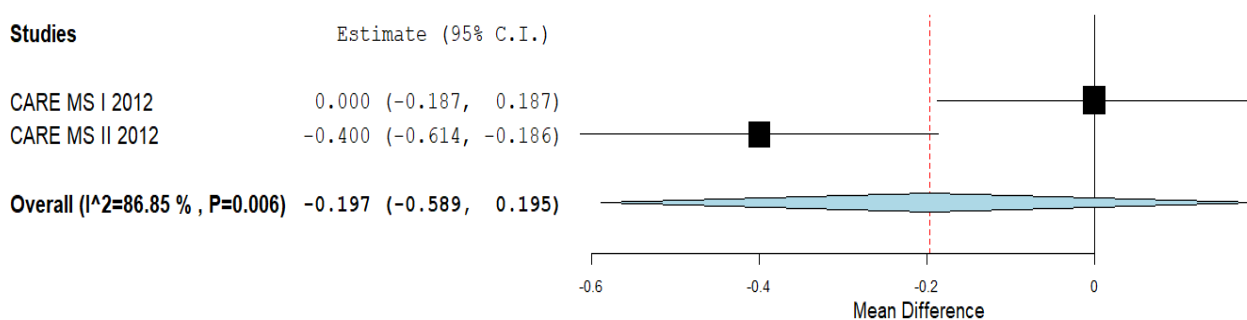**Table 5.** Comparison of mean EDSS score change from baseline at 24 months

Figure 5. Forest plot of comparison of mean EDSS score change from baseline at 24 months

4.7 Number of participants with new T2-hyperintense lesions on MRI at 24 months

The two trials assessed the number of participants with new T2-hyperintense lesions on MRI. Results for alemtuzumab 12 mg versus IFN beta 1a were reported. Since Q was equal to 4,184, there was significant heterogeneity across studies, so the RE model should be used. There was a significant difference in favour of alemtuzumab (OR 0.53, 95% CI 0.31 to 0.90), p=0.018).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	176/363	99/172	49.95%	0.69(0.48-1.00)
CARE MS II	186/403	127/187	50.05%	0.41(0.28-0.58)

Table 6. Comparison of number of participants with new T2-hyperintense lesions on MRI at 24 months
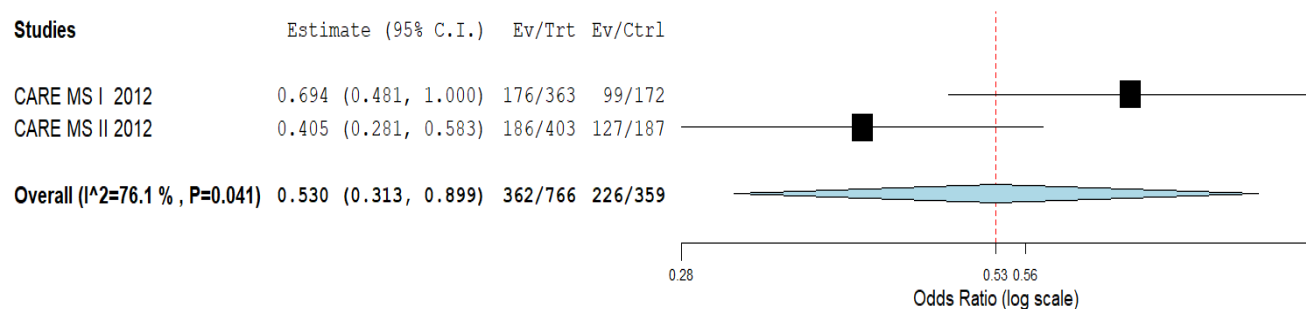

Figure 6. Forest plot of comparison of number of participants with new T2-hyperintense lesions on MRI at 24 months

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4.8 Number of participants experiencing treatment discontinuation caused by adverse events

The two trials assessed the number of participants who experienced treatment discontinuation caused by adverse events. Results for alemtuzumab 12 and 24mg versus IFN beta 1a were reported. Since Q was equal to 0,960, there was not significant heterogeneity across studies, so the FE model should be used. There was a significant difference in favour of alemtuzumab (OR 0.33, 95% CI 0.18 to 0,61), p<0.001).

STUDY	Alemtuzumab	Interferon beta 1A	WEIGHT	ODDS RATIO
CARE MS I	5/376	11/187	42.24%	0.22(0.07-0.63)
CARE MS II	14/435	15/202	57.76%	0.42(0.20-0.88)

Table 7. Comparison of number of participants experiencing treatment discontinuation caused by adverse events
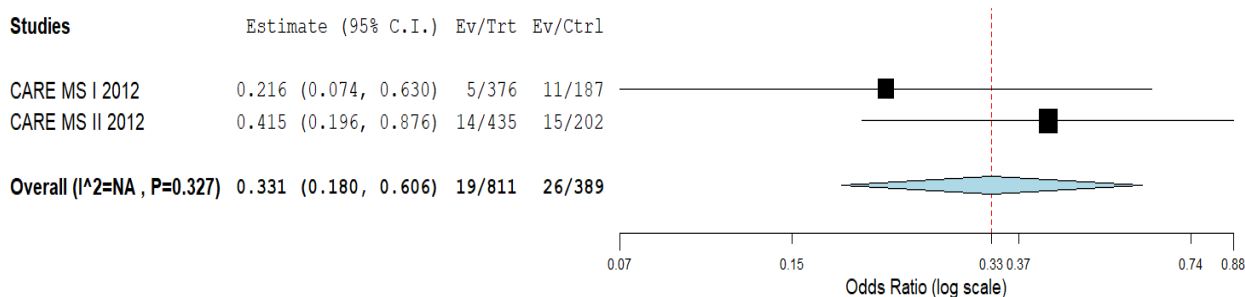

Figure 7. Forest plot of comparison of number of participants experiencing treatment discontinuation caused by adverse events

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5. CONCLUSION

Alemtuzumab was proven to be more effective than IFN beta 1a. This meta- analysis compared the benefit and safety of alemtuzumab versus IFN beta 1a in the treatment of people with RRMS. A total of 1191 patients were included in it, 802 allocated to receive Alemtuzumab and 389 IFN beta 1a. In safety assessments, 811 patients received Alemtuzumab and 389 IFN beta 1a.. The results showed statistically significant differences favouring alemtuzumab in reducing relapses at 24 months (54% less chance of relapse when treated with alemtuzumab)., in preventing disease progression (37% less chance of relapse at 24 months when treated with alemtuzumab, in the changes of EDSS score (disability progression is decreased 0.20 points less with alemtuzumab compared to interferon beta 1a) and in developing new T2 lesions on MRI over 24 months' follow-up (47% less chance of developing new T2 hyperintense lesions on MRI when treated with alemtuzumab). The rates of adverse events were similarly high for both treatments. However, fewer patients in the alemtuzumab group experienced treatment discontinuation caused by adverse events (67% less chance of treatment discontinuation when treated with alemtuzumab).

5.1 Limitations of the study

Clinical trials involved in this meta- analysis were limited, due to the fact that only three clinical trials comparing efficacy, tolerability and safety of alemtuzumab with INF beta 1a have taken place. As a result, funnel plots could not be used to explore possible publication bias, nor a sensitivity analysis could be applied in order to determine the robustness of the observed outcomes.

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