Decision Making in MS INF and GA

Abdorreza Naser Moghadasi

MS Research Center

- Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) with a highly variable clinical course.

- The current classification distinguishes between relapsing and progressive forms of the disease.

- Relapsing forms (RFMS) are characterized by clearly defined attacks of new or increasing neurological symptoms.

- However, at subclinical threshold, these patients show in magnetic resonance imaging (MRI) new T2 and/or Gadolinium enhancing lesions

- In contrast, progressive forms are characterized by worsening neurological function (accumulation of disability) since the onset of symptoms (primary progressive MS) or after a relapsing remitting phase (secondary progressive MS)

- Neurodegeneration probably begins from the first inflammatory events, but due to brain reserve and compensatory mechanisms, it may not always be clinically evident.

- However, in light of such evidence (showing an early and intensive axonal and neuronal damage), the idea of RFMS as a benign disease cannot be more accepted

- In recent years, compelling data has shown the possibility to suppress the inflammatory activity of RFMS by new and potent anti-inflammatory drugs.

- But, all of these therapies focus on the immune system, mostly in the periphery, and they are not able to prevent neurodegeneration directly.

- Due to their only indirect antineurodegenerative effects, these drugs should be used in their best therapeutic window of opportunity, when inflammation plays a significant role.

- The actual MS treatment paradigm pursues the early control of the inflammatory aspects of the disease, which are defined by clinical relapses and MRI activity.

- RFMS drugs are categorized in different categories of efficacy and burden of therapy, with the possibility to do therapeutic switches in the case of therapeutic failure or safety alarms

- Cancer is a monophasic, mostly fatal, disease while MS shows extreme variability along its long-term course.

- Moreover, the biological system(s) in cancer, which should be target by therapy (ies), are usually well defined, in MS still not

- The ability of monitoring the disease activity in cancer let the clinicians to identify early responders and non responders to therapy.

- That is not the actual reality for MS, where the identification of active patients and the monitoring of disease activity remain a challenge

- A personalized treatment approach in MS (tailoring therapies on MS characteristics of the individual patient) is our future aim

P T. 2010 OCT; 35(10): 542.
THE FIVE RIGHTS
A DESTINATION WITHOUT A MAP
MATTHEW GRISSINGER, RPH, FASCP

- **the right patient,**
- **the right drug,**
- **the right time,**
- **the right dose,**
- **and the right route**

J Neurol Neurosurg Psychiatry. 2017 Aug;88(8):621-625.

Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study.

Lunde HMB[1], Assmus J[2], Myhr KM[1,3], Bø L[1,4], Grytten N[4].

- Median life expectancy was 74.7 years for MS and 81.8 years for the general population ($p<0.001$); 77.2 years for women with MS and 72.2 years for men with MS ($p<0.001$).

- A rise in survival in MS was observed during the entire observation period.

Neurol Neuroimmunol Neuroinflamm. 2018 Sep 13;5(6):e498.

Rituximab-induced hypogammaglobulinemia in patients with neuromyelitis optica spectrumd isorders.

Marcinnò A[1], Marnetto F[1], Valentino P[1], Martire S[1], Balbo A[1], Drago A[1], Leto M[1], Capobianco M[1], Panzica G[1], Bertolotto A[1].

- RTX reduced total IgG by 0.42 g/L per year, IgA by 0.08 g/L per year, and IgM by 0.07 g/L per year. Hypogammaglobulinemia(hypo-IgG) (IgG < 7 g/L) developed in 11/15 patients.

- Severe hypo-IgG (IgG < 4 g/L) was found in 3/15 patients, of whom 2 patientsdeveloped serious infectious complications.

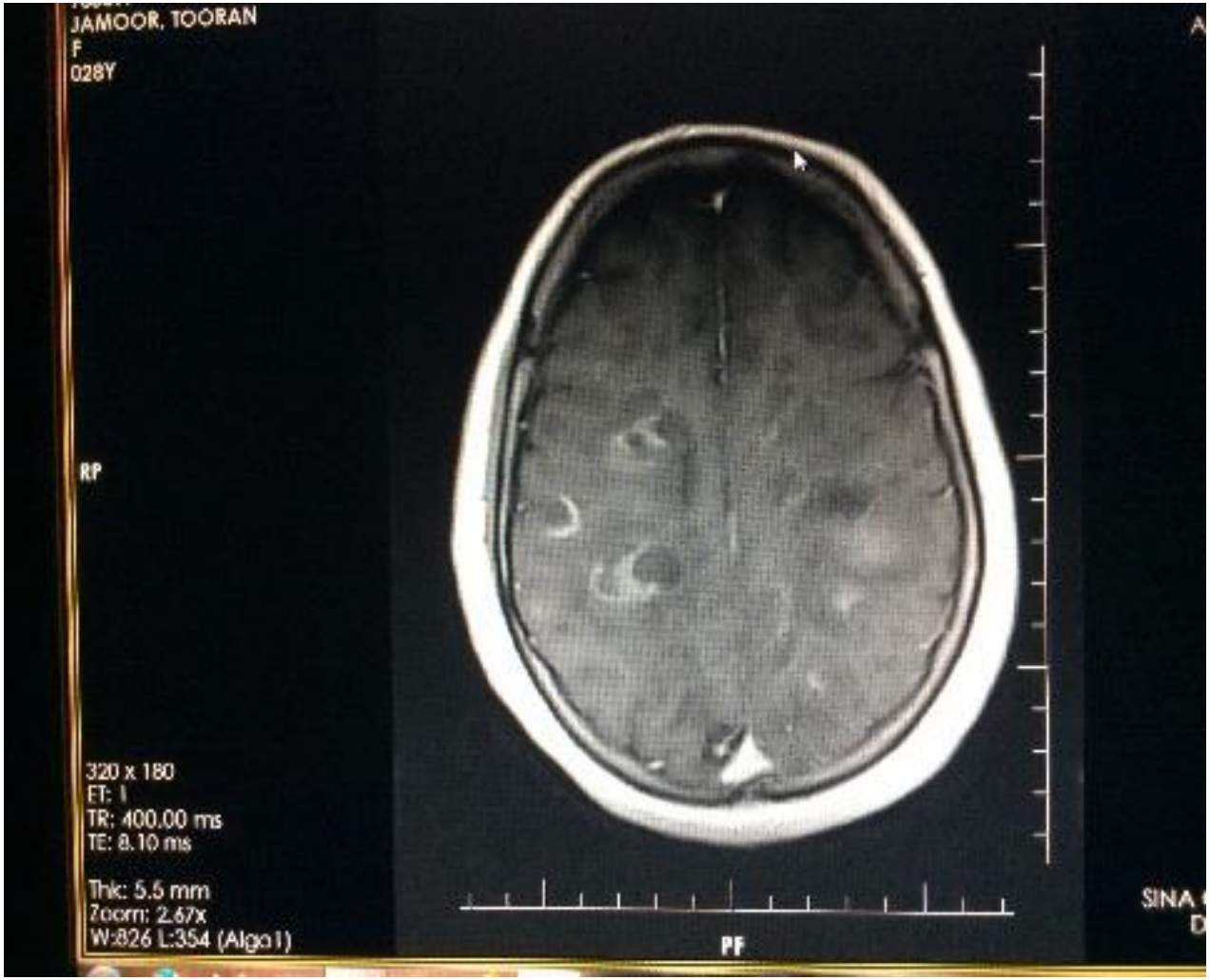
- Results obtained in this study suggest the importance of monitoring total and specific Ig levels before and during treatment with anti-CD20 drugs to prevent hypo-Ig-related complications and to optimize clinical management.

- J Invest Dermatol. 2015 Oct 5.
  Dimethylfumarate Impairs Neutrophil Functions.
  Müller S[1], Behnen M[2], Bieber K[1], Möller S[2], Hellberg L[2], Witte M[1], Hänsel M[1], Zillikens D[1], Solbach W[2], Laskay T[2], Ludwig RJ[1]

- The patient is a 30-year old female a known case of MS from 2011.

- Interferon beta 1b started for and she was more or less stable till 2013, when she developed a sever exacerbation

- Fingolimod started for her after first dose observation and she was stable for 12 months.
- The patient stopped Fingolimod usage due to pregnancy planning.
- The patient experienced a sever relapse 25 days following Fingolimod discontinuation and admitted for further evaluation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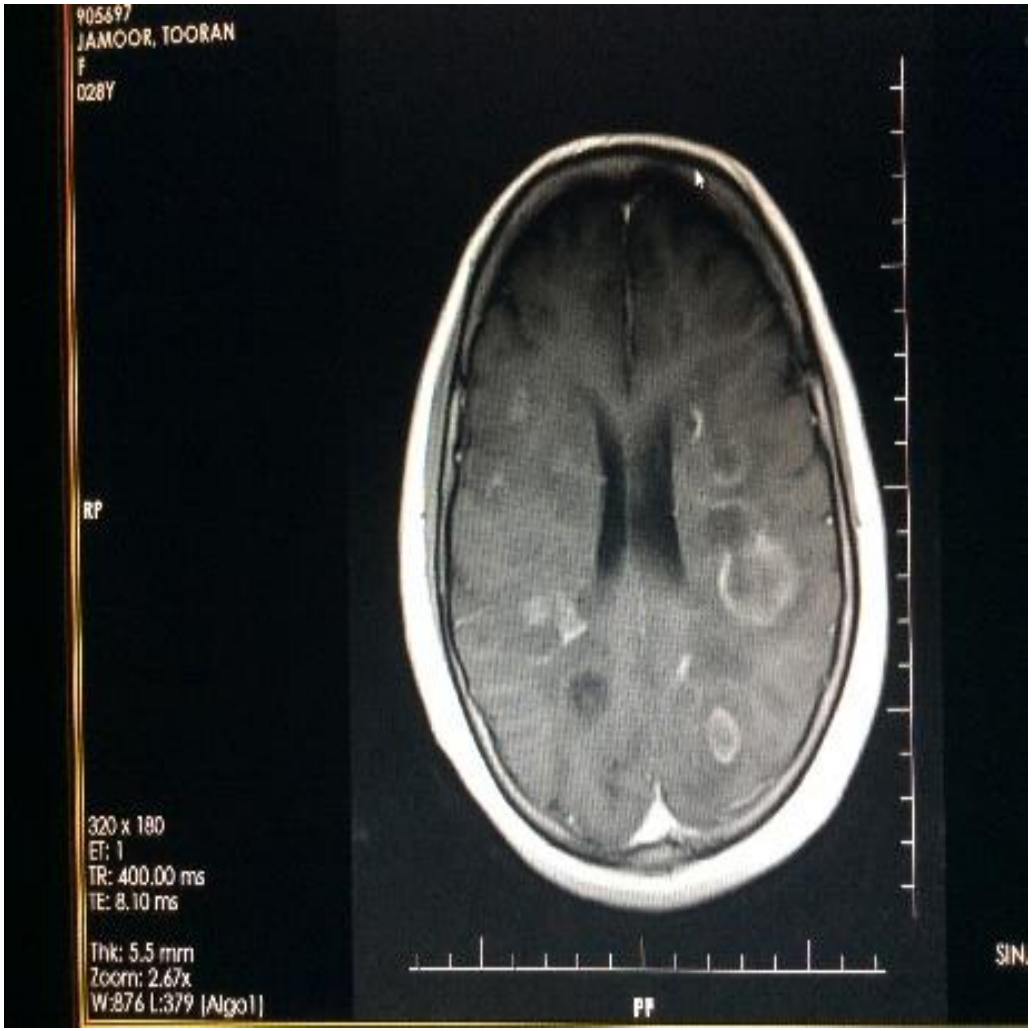
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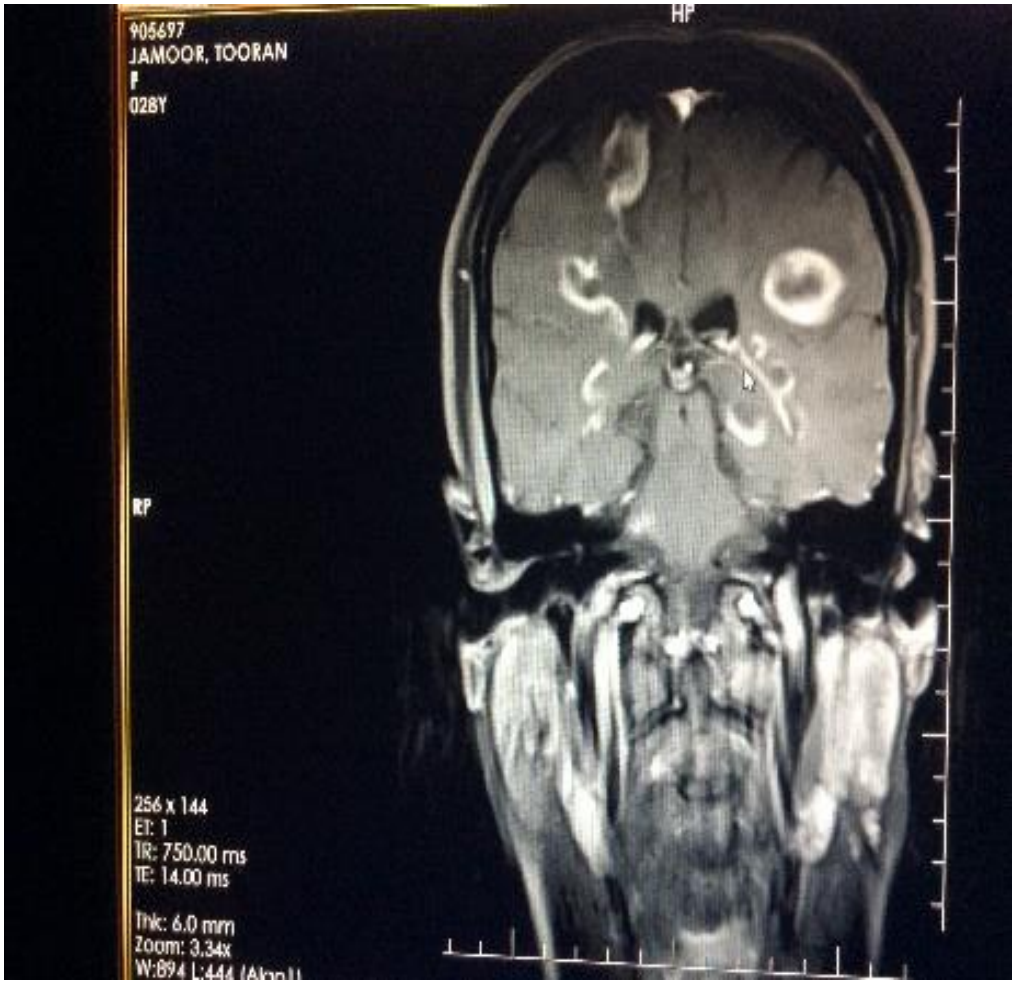
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Brain Behav. 2017 May 8;7(6):e00696.
The innovative development in interferon beta treatments of relapsing-remitting multiple sclerosis.
Madsen C.

- Acknowledging that until 20 some years ago the treatment of MS patients focused mainly on treating relapses with systemic corticosteroids and providing various symptomatic treatment, the introduction of interferon beta therapies in 1993 (interferon beta-1b) and in 1996 (interferon beta-1a) fundamentally changed the MS treatment paradigm

- For patients, treatment transferred from symptomatic management into disease modifying long-term therapy, and for neurologists their roles changed from passively observing and awaiting patient worsening into proactively treating the underlying disease in the MS patients.

- Since then several other DMTs have been approved for the treatment of MS.

- However, with a growing body of evidence on the long-term benefits by reduction of disability progression, reduced mortality, and data to suggest maternal and fetal relative safety in pregnancy outcomes — interferons maintain an important role in the treatment of RRMS

- interferon beta therapies have been shown to reduce the number of relapses by an average of 30% compared to placebo and in particular the number of severe relapses is reduced.

- Furthermore, interferon beta delays the development of permanent neurological disability and disease activity evaluated by magnetic resonance imaging (MRI).

- Treatment with interferon beta prolongs the time to CDMS and reduces relapse rate and disease progression.

- Retrospectively, it proved itself to be a clinical paradox that the window of opportunity for obtaining maximum benefit from the DMT was narrowed considerably over time.

- On one hand a patient with little or no current disease activity (i. e., relapse) was ineligible to receive interferon beta, however, after subsequently experiencing disability progression following a relapse, the patient was at risk of having missed the opportunity for receiving disease modifying treatment.

- Fortunately, treatment with interferon beta is initiated earlier

Pharmacodynamic properties of interferons in MS

- Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers.

- Interferons are cytokines that mediate antiviral, anti-proliferative, and immunomodulatory activities.

- Three major forms of interferons have been distinguished: alpha, beta, and gamma.

- Interferons alpha and beta are classified as Type I interferons and interferon gamma is a Type II interferon.

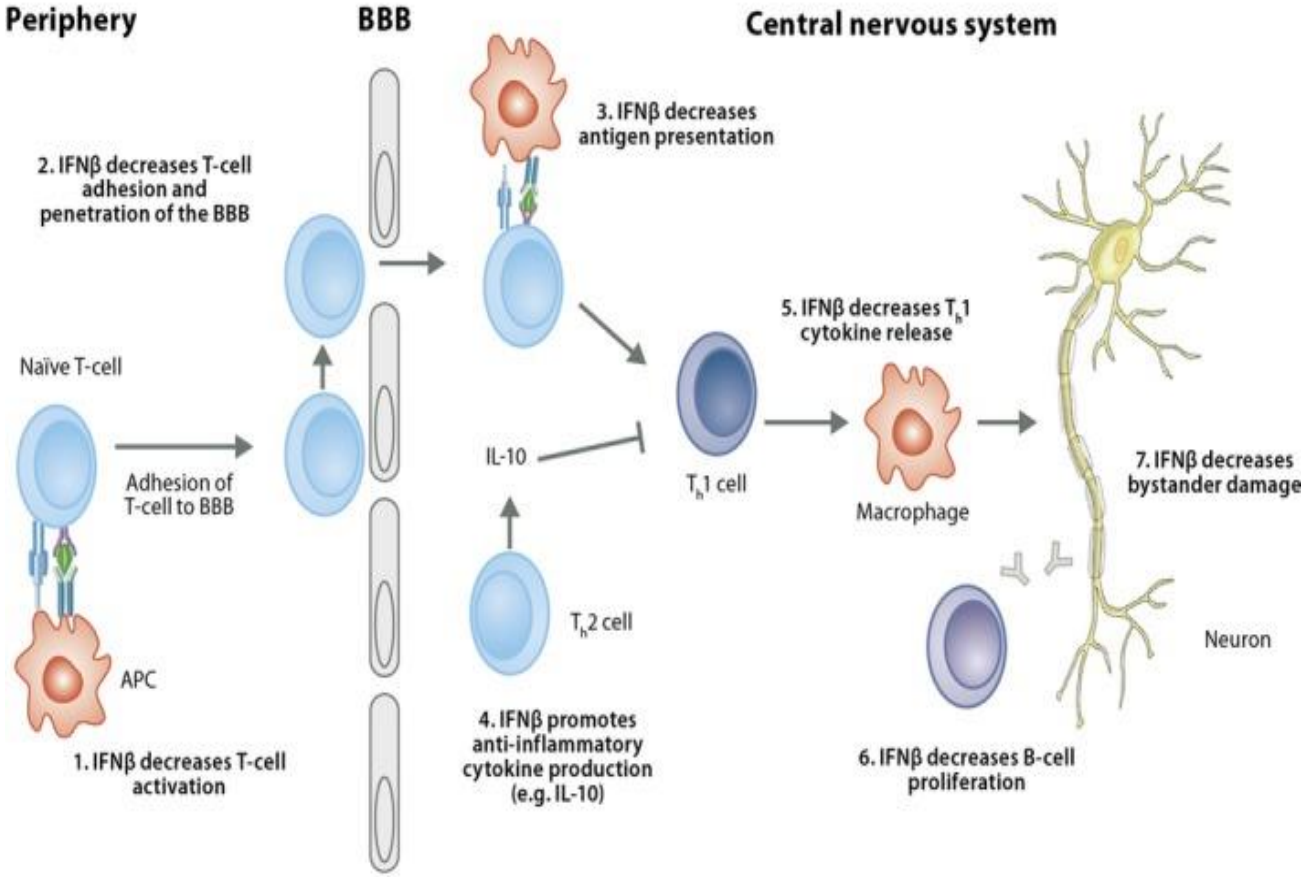
- The mechanism of action of interferon beta is complex, involving effects at multiple levels of cellular function.

- Interferon beta appears to directly increase expression and concentration of anti-inflammatory agents while down regulating the expression of proinflammatory cytokines.

- Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells.

- This binding initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers.

There are several proposed mechanisms of action for IFNβ in MS



Ag=antigen; APC=antigen-presenting cell; BBB=blood-brain barrier ; IFN=interferon; IL=interleukin; MMP=matrix metalloproteinase; MS=multiple sclerosis; TH=T helper cell
Figure adapted from: Wiendl H et al. Expert Opin Investig Drugs 2003;12:689–712

Int J Mol Sci. 2015 Jul 6;16(7):15271-86.
Interferon Beta-1a (AVONEX®) as a Treatment Option for Untreated Patients with Multiple Sclerosis (AXIOM): A Prospective, Observational Study.
Kleinschnitz C, Niemczyk G, Rehberg-Weber K, Wernsdörfer C.

- RRMS patients with a treatment-free interval of at least three months were included and treated with IFNb-1a for up to 12 months.

- Relapse rate, disability progression, injection-related parameters and quality of life observed during the prospective part were compared with retrospectively-collected data.

- Two hundred and thirty five RRMS patients participated in AXIOM.
- The mean relapse rate decreased from 1.1 in the three months before baseline to 0.2 per quarter during the twelve-month observational period
- MSFC improved during twelve months of IM IFNb-1a treatment, while the EDSS did not change over the course of this study.

J Neurol Sci. 2014 Jul 15;342(1-2):16-20.

Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferonbeta: a randomized clinical trial.

Mokhber N[1], Azarpazhooh A[2], Orouji E[3], Rao SM[4], Khorram B[5], Sahraian MA[6], Foroghipoor M[3], Gharavi MM[7], Kakhi S[8], Nikkhah K[9], Azarpazhooh MR[3].

- Ninety newly diagnosed, definite MS subjects referred to Ghaem Medical Center, Mashhad, Iran, were enrolled into this study between 2006 and 2009.

- They were randomly categorized into three DMT groups; Avonex, Rebif and Betaferon.

- Cognition status was assessed in MS patients at baseline and 12 months after treatment with DMTs using the 5 tests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).

- The Symbol Digit Modalities Test scores improved in all groups at 12 month vs. baseline (Avonex: 34.50 vs. 38.95, p=0.011; Rebif: 35.30 vs. 40.13, p=0.001; Betaferon: 26.18 vs. 29.32, p=0.029).

- The Selective Reminding Test (SRT)-Total, the 10/36-Delay, and the Paced Auditory Serial Addition Test-Easy were improved in Avonex and Rebif but not in Betaferon group.

- The SRT-Delay and Word List Generation were improved only in the Avonex group.

- There was no significant difference in other components of the BRB-N among these three treatment groups.

- Different types of DMTs may improve some aspects of cognitive function in patients with MS.

- Treatment with Avonex and Rebif (Interferon beta-1a preparations) were more helpful in resolving the cognitive impairments in MS patients compared to Betaferon (Interferon beta-1b) as investigated in this study.

Clin Neurol Neurosurg. 2012 Sep;114(7):986-9.

Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial.

Nafissi S, Azimi A, Amini-Harandi A, Salami S, shahkarami MA, Heshmat R.

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- 31 patients (mean±SD of age=33.7±7.0; 7 males and 24 females) in the Avonex and 29 patients (mean±SD of age=32.2±9.2; 8 males and 21 females) in the CinnoVex group completed full 24 months of study period.

- Decrease in EDSS was 1.05±0.24, p=0.62 in the Avonex and 0.16±0.88, p=1.0 in the CinnoVex group after 12 months and 0.27±1.05, p=0.46 in the Avonex and 0.16±1.06, p=1.0 in the CinnoVex group after 24 months.

- There was no statistically significant difference in attack number between two groups .
- Volume of T2-weighted lesions on MRI showed a progressive significant increase in the 12th month in Avonex treated patients compared with first image ($p=0.01$).
- But number of gadolinium-enhancing lesions in CinnoVex showed statistically significant decrease after 12 months.
- However, there were no significant differences between groups after 24 months.

J Res Pharm Pract. 2016 Jul-Sep;5(3):181-5.

Quality of life in relapsing-remitting multiple sclerosis patients receiving CinnoVex compared with Avonex.

Hatam N[1], Bastani P[2], Shahtaheri RS[3].

- MS groups did not differ in physical and mental health composite scores as well as relative scales.

- The results of regression models for each subscale showed that age, marriage, and Expanded Disability Status Scale were associated with several subscales of the MSQoL-54 ($P < 0.05$).

Lancet. 1998 Nov 7;352(9139):1498-504.
Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group.

- 560 patients with EDSS scores of 0-5.0, from 22 centres in nine countries, were randomly assigned subcutaneous recombinant interferon beta-1a 22 microg (n=189), or 44 microg (n=184), or placebo (n=187) three times a week for 2 years.

- All patients had MRI twice yearly and 205 had monthly scans in the first 9 months of treatment.

- The relapse rate was significantly lower at 1 and 2 years with both doses of interferon beta-1a than with placebo.

- Time to first relapse was prolonged by 3 and 5 months in the 22 microg and 44 microg groups respectively, and the proportion of relapse-free patients was significantly increased ($p<0.05$).

- Interferon beta-1a delayed progression in disability, and decreased accumulated disability during the study.

- The accumulation of burden of disease and number of active lesions on MRI was lower in both treatment groups than in the placebo group.

- Subcutaneous interferon beta-1a is an effective treatment for relapsing/remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures in a dose-related manner, and it is well tolerated.

PLoS One. 2014 Mar 13;9(3):e91098. doi: 10.1371/journal.pone.0091098. eCollection 2014.

Effect of treatment with interferon beta-1a on changes in voxel-wise magnetization transfer ratio in normal appearing brain tissue and lesions of patients with relapsing-remitting multiple sclerosis: a 24-week, controlled pilot study.

Zivadinov R, Dwyer MG, Markovic-Plese S, Kennedy C, Bergsland N, Ramasamy DP, Durfee J, Hojnacki D, Hayward B, Dangond F, Weinstock-Guttman B.

- The significant change in NABT volume with increasing VW-MTR at 12 weeks suggests that active remyelination in patients with RRMS may occur during treatment with IFN ß-1a SC.

- Findings from two patients with the highest number of Gd-enhancing lesions at baseline suggest that extensive remyelination in NABT may occur in patients with high disease activity.

J Neurol. 2004 Sep;251 Suppl 5:v42-v49.

Importance of benefit-to-risk assessment for disease-modifying drugs used to treat MS.

Francis GS

- Evidence-based medicine approaches treatment effect by determining the number of patients who must be treated in order to achieve a desired outcome (NNT)

- In MS, this can be avoiding a relapse or maintaining an additional patient relapse-free, or maintaining an additional patient progression-free.

- Generally, NNT and NNH (number needed to harm, i. e., the number of patients needed to treat for an adverse outcome) values are rounded up to the next integer.

- For NNT, lower values indicate better outcomes than higher values.
- For NNH, higher values are better than lower values.

Table 5 NNT[a] values based on efficacy outcome data for products approved as first-line therapy in relapsing multiple sclerosis

Outcome	IFN β-1b, 8 MIU on alternate days	IFN β-1a, 30 mcg qw	Glatiramer acetate, 20 mg once daily	IFN β-1a, 22 mcg tiw	IFN β-1a, 44 mcg tiw	IFN β-1a, 44 mcg tiw versus 30 mcg qw
Relapse count						
1 year	nr	11	nr	2.0	1.6	10
2 years[b]	2.3	7	4.1	2.7	2.4	10[f]
Relapse-free (%)						
1 year	nr	nr	16[d]	4	3	11
2 years[b]	12/6[e]	9[f]	15	10	6	13[c]
Progression-free (%)	13	8	33	13	10	100
No T1 active scans (%)	–	9[g]	14[d]	3.7[d]	3.1[d]	6[h]

[a] NNT values < 5.0 are taken to one decimal place to allow discrimination between regimens; values > 5.0 are rounded up to the next highest integer; [b] NNT per year based on annualised rate over 2 years; [c] 64-week data; [d] 9-month data; [e] higher value derived from package insert based on regulatory review of data, lower value from publication (see text); [f] applies to subset (57 %) completing 2 years on study; [g] 12-month data; [h] 24-week data

IFN interferon; *NNT* number of patients needed to treat to obtain benefit; *nr* not reported; *qw* once weekly; *tiw* three times weekly; – not obtained

Table 6 Safety outcomes, expressed as NNH, for products approved as first-line therapy in relapsing multiple sclerosis

Outcome	IFN β-1b, 8 MIU on alternate days	IFN β-1a, 30 mcg qw	Glatiramer acetate, 20 mg once daily	IFN β-1a, 22 mcg tiw	IFN β-1a, 44 mcg tiw	IFN β-1a, 44 mcg tiw versus 30 mcg qw
All dropouts	125	38	59	33	100	44
Dropouts due to adverse events	14	33	21	48	27	334

IFN interferon; *NNH* number of patients needed to harm, defined as an adverse event-related dropout; *qw* once weekly; *tiw* three times weekly

- As can be seen from the tables, the IFN products have consistently lower NNT values than GA, suggesting that IFN is more effective as an MS therapy.

- In addition, the IFN products have substantially lower NNT than NNH values, regardless of definitions used, indicating a favourable benefit-to-risk ratio compared with placebo.

J Neurol Neurosurg Psychiatry. 2017 Apr;88(4):285-294.
Subcutaneous interferon b-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLEXION study.
Comi G[1], De Stefano N[2], Freedman MS[3], Barkhof F[4,5], Uitdehaag BM[6], de Vos M[7], Marhardt K[8], Chen L[9], Issard D[10], Kappos L[11].

- Early treatment following a first clinical demyelinating event (FCDE) delays further disease activity in patients with multiple sclerosis (MS).

- This study determined the effects of early versus delayed treatment (DT) with subcutaneous interferon (sc IFN) ß-1a 44 µg in patients with an FCDE up to 60 months postrandomisation.

- Patients who completed the 24-month double-blind REFLEX (REbif FLEXible dosing in early MS) study entered an extension (REFLEXION, REbif FLEXible dosing in early MS extensION):
- patients initially randomised to sc IFN ß-1a and not reaching clinically definite MS (clinically definite MS, CDMS (second attack or EDSS increase) continued original treatment (three times weekly (tiw) or once weekly (qw)); placebo patients switched to tiw (DT); patients with CDMS switched to tiw.

- At month 60, cumulative probability of CDMS was: DT 44.6%; qw 40.7% (nominal p=0.084 vs DT); tiw 39.2% (nominal p=0.032 vs DT).

- Cumulative probability of McDonald MS conversion (CDMS or new MRI activity) at month 60 was also reduced for tiw versus DT (nominal $p<0.001$).

- At month 60, mean cumulative numbers of new T2, gadolinium-enhancing and T1 hypointense lesions were lower with sc IFN ß-1a qw (nominal $p<0.05$) and tiw versus DT (nominal $p<0.001$); T2 and T1 hypointense lesion volume change was lower for sc IFN ß-1a tiw versus DT (nominal $p<0.01$).

- Over 5 years in patients presenting with an FCDE, early sc IFN ß-1a tiw administration versus DT prolonged time to CDMS and McDonald MS, and reduced overall MRI activity.

Ther Adv Neurol Disord. 2017 Jan;10(1):18-32.
Cognition and fatigue in patients with relapsing multiple sclerosis treated by subcutaneous interferon b-1a: an observational study SKORE.
Benešová Y[1], Tvaroh A[2].

- Fatigue is probably the most common symptom, with up to 90% of MS individuals reporting fatigue at some point.

- Cognitive impairment affects about 50% of patients and may be present at all MS stages.

- Cognition status was assessed using the Paced Auditory Serial Addition Task (PASAT), fatigue using the Fatigue Descriptive Scale (FDS), and disability using the Expanded Disability Status Scale (EDSS), at baseline, and after 6, 12 and 24 months.

- The proportion of patients with cognitive improvement was higher compared with those with a stable or decreased PASAT scores at all time points, and the average cognitive performance improved during the follow-up period.

- Also the proportion of patients with stable or improved fatigue and EDSS scores was higher compared with those in which FDS or EDSS scores declined, this was found at all time points of the analysed sample.

- However, the direct effect of IFN ß-1a on cognition and fatigue cannot be concluded from this study.

J Neurol Neurosurg Psychiatry. 2015 Nov;86(11):1202-7.
Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15.
Kappos L, Kuhle J, Multanen J, Kremenchutzky M, Verdun di Cantogno E, Cornelisse P, Lehr L, Casset-Semanaz F, Issard D, Uitdehaag BM.

- An exploratory study of the relationship between cumulative exposure to subcutaneous (sc) interferon (IFN) β-1a treatment and other possible prognostic factors with long-term clinical outcomes in relapsing-remitting multiple sclerosis

- Patients in the original PRISMS study were invited to a single follow-up visit 15 years after initial randomisation (PRISMS-15).

- Outcomes over 15 years were compared in the lowest and highest quartile of the cumulative sc IFN β-1a dose groups, and according to total time receiving sc IFN β-1a as a continuous variable per 5 years of treatment.

- Most patients with RRMS (>80%) will develop secondary–progressive MS (SPMS) over 25 years,with a median time to progression ranging from approximately 15–21 years after disease onset.
- Owing to the lifelong course of MS, it is important to determine potential baseline or early prognostic factors for long-term outcomes.

- Higher cumulative dose exposure and longer treatment time appeared to be associated with better outcomes on: annualised relapse rate, number of relapses, time to Expanded Disability Status Scale (EDSS) progression, change in EDSS, proportions of patients with EDSS ≥ 4 or ≥ 6, ≤ 5 relapses and EDSS <4 or <6, and time to conversion to secondary-progressive MS (SPMS).

- Higher dose exposure was associated with lower proportions of patients with EDSS progression and conversion to SPMS, and longer time on treatment with lower risk of first relapse

- Change in EDSS from baseline to 24 months was a strong predictor of evaluated clinical outcomes over 15 years.

- These findings suggest that higher cumulative exposure to sc IFN ß-1a may be associated with better clinical outcomes, and early change in EDSS score may have prognostic value, over many years, in RRMS.

- In the MAX cumulative dose group, only 20.8% of patients had converted to SPMS over 15 years, compared with 52.1% in the MIN dose group

- The positive association of higher treatment exposure with more favourable outcomes suggests that starting treatment early and maintaining adherence over the long term may be important for optimal clinical outcomes

Expert Opin Drug Deliv. 2017 Dec 5:1-9.

Ease of use of two autoinjectors in patients with multiple sclerosis treated with interferon beta-1a subcutaneously three times weekly: results of the randomized, crossover REDEFINE study.

Wray S[1], Hayward B[2], Dangond F[2], Singer B[3].

- Of 97 randomized patients, 29 had most recent experience with manual injection; 23 with single-use autoinjector; and 45 with reusable autoinjector.
- 68.4% found using the single-use autoinjector very easy or easy, versus 77.9% for the reusable device (difference -9.5%; p = 0.200).
- 40.0% versus 29.5% found the respective devices very easy (difference 10.5%; p = 0.203).

Neurology. 1995 Jul;45(7):1268-76.

Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group.

Johnson KP[1], Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB.

- Two hundred fifty-one patients were randomized to receive copolymer 1 (n = 125) or placebo (n = 126) at a dosage of 20 mg by daily subcutaneous injection for 2 years.

- The final 2-year relapse rate was 1.19 +/- 0.13 for patients receiving copolymer 1 and 1.68 +/- 0.13 for those receiving placebo, a 29% reduction in favor of copolymer 1 (p = 0.007) (annualized rates = 0.59 for copolymer 1 and 0.84 for placebo).

- Trends in the proportion of relapse-free patients and median time to first relapse favored copolymer 1.

- When the proportion of patients who improved, were unchanged, or worsened by > or = 1 EDSS step from baseline to conclusion (2 years) was evaluated, significantly more patients receiving copolymer 1 were found to have improved and more receiving placebo worsened ($p = 0.037$).

- Patient withdrawals were 19 (15.2%) from the copolymer 1 group and 17 (13.5%) from the placebo group at approximately the same intervals.
- The treatment was well tolerated.
- The most common adverse experience was an injection-site reaction.
- Rarely, a transient self-limited systemic reaction followed the injection in 15.2% of those receiving copolymer 1 and 3.2% of those receiving placebo.

Ann Neurol. 2011 Jan;69(1):75-82.
Phase III dose-comparison study of glatiramer acetate for multiple sclerosis.
Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M; FORTE Study Group.

- To evaluate the safety, tolerability, and efficacy of glatiramer acetate (GA) 40 mg compared to a 20mg dose

- Patients with MS with ≥ 1 documented relapse in 12 months prior to screening, or ≥ 2 documented relapses in 24 months prior to screening, and EDSS score 0 to 5.5 were enrolled.

- A total of 1,155 patients randomized to GA 20 mg (n = 586) or 40 mg (n = 569).
- The groups were well-matched at baseline on demographic, clinical, and MRI characteristics.
- The primary endpoint was similar in both groups with mean ARR of 0.33 for the 20 mg group, 0.35 for the 40 mg group, and 0.27 for patients from both groups who completed the entire 1-year treatment.

- A total of 77% of patients remained relapse-free in both groups.

- Both groups showed a reduction in mean number of gadolinium-enhancing and new T2 lesions over time with trend for faster reduction in the first trimester with the 40 mg dose compared with 20 mg dose.

- Both doses were well-tolerated with a safety profile similar to that observed in previous studies of 20 mg GA.

- In relapsing-remitting MS patients, both the currently-approved GA 20 mg and 40 mg doses were safe and well-tolerated, with no gain in efficacy for the higher dose.

Ann Neurol. 2013 Jun;73(6):705-13.

Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis.

Khan O[1], Rieckmann P, Boyko A, Selmaj K, Zivadinov R; GALA Study Group.

- This randomized, double-blind study was conducted in 142 sites in 17 countries.

- Patients with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an EDSS≤ 5.5, were randomized 2:1 to receive either sc GA 40mg tiw (1ml) or placebo for 12 months.

- Of 1,524 patients screened, 1,404 were randomized to receive GA 40mg sc tiw (n = 943) or placebo (n = 461).

- Ninety-three percent and 91% of patients in the placebo and GA groups, respectively, completed the 12-month study.

- GA 40mg tiw was associated with a 34.0% reduction in risk of confirmed relapses compared with placebo (mean ARR= 0.331 vs 0.505; $p < 0.0001$).

- Patients who received GA 40mg tiw experienced highly significant reduction ($p < 0.0001$) in the cumulative number of gadolinium-enhancing T1 (44.8%) and new or newly enlarging T2 lesions (34.7%) at months 6 and 12.

- GA 40mg tiw was safe and well tolerated. The most common adverse events in the GA group were injection site reactions (35.5% with GA vs 5.0% with placebo).

Mult Scler. 2016 Aug 8.

Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study.

Khan O[1], Rieckmann P[2], Boyko A[3], Selmaj K[4], Ashtamker N[5], Davis MD[6], Kolodny S[7], Zivadinov R[8].

- GA is a first-line therapy approved for the treatment of RRMS that has a well-characterized long-term safety profile and established efficacy, with more than 2 million patient-years of overall exposure to glatiramer acetate 20mg/mL administered daily by subcutaneous injection (GA20)

- Like other first-line treatment regimens in RRMS, GA20 requires long term injection of the drug and can be associated with injection-related adverse events , which may diminish adherence in some patients

- This is of particular importance because treatment adherence ensures optimal clinical outcomes

- Modified treatment regimens with proven, long-term clinical efficacy have the potential to minimize adverse side effects while maintaining efficacy, thereby supporting appropriate adherence to treatment and eliciting greater overall clinical benefit

- Participants who completed the 1-year PC phase of the GALA study were eligible to receive GA40 treatment in an ongoing open-label (OL) extension study and were invited to switch to or continue the GA40 regimen.

- This clinical assessment of GA40 will provide further insight into the value of the three-times weekly dosing regimen in the treatment of RRMS.

- During the PC phase, eligible patients were randomized 2:1 to receive GA40 or placebo and seven scheduled site visits occurred: at screening, baseline (Month 0), and Months 1, 3, 6, 9, and 12.

- A complete neurological and physical examination was performed every 6 months, and ECGs, safety laboratory tests, and serum pregnancy tests were performed annually.

- MRI scans were performed at baseline, Month 6, Month 12, and Month 36 of the study.

- Adverse events and the use of concomitant medications were monitored throughout the study.

- The primary endpoint of the PC phase was the ARR, defined as the total number of confirmed relapses divided by the annual exposure to study drug.

- Additional clinical endpoints included time to first relapse, time to 6-month confirmed disability progression (CDP), and time to 6-month confirmed EDSS 4

- MRI endpoints included number of GdE T1 lesions, number of new or enlarging T2 lesions, percent brain volume change from baseline to Month 36 and from Months 12 to 36, and percent change in GM and WM volumes from baseline to Month 36 and from Months 12 to 36.

- A total of 716 (75.9%) ES patients and 325 (70.5%) DS patients completed 3 years of follow-up, and 562 (59.6%) ES patients and 260 (56.4%) DS patients completed the Year 3 MRI scan.

- Most discontinuations in the OL phase were due to withdrawal of consent (143 (11%) in all OL patients: 84 (10%) in ES and 59 (14%) in DS group).
- Of these patients, 141 offered additional insight into the reason for withdrawal of consent with "patient decision" (53 of 141 responses) and "lack of efficacy"

- Time to first relapse was significantly longer in ES patients compared with DS patients.

- Overall, there were low disability event rates, with 11% of ES patients and 13% of DS patients experiencing 6-month CDP during the entire study, including the PC and OL phases.

- There were similarly low progression rates for 6-month confirmed EDSS 4 with 3% of ES patients and 5% of DS patients

- The number of GdE T1 lesions and new or enlarging T2 lesions was significantly lower for ES patients than for DS patients over the first year of treatment, when evaluated at Months 6 and 12.

- During the OL extension phase, following the conversion from placebo to GA40 in the DS group, lesion counts were similar between ES patients and DS patients at Year 3.

- During the core phase, there were no statistical differences between ES and DS patients in adjusted mean PBVC, adjusted mean WM volume change or adjusted mean GM volume change.

- In the OL phase, there was a trend toward a decreased loss of whole-brain volume in ES patients compared with DS patients.

- At Month 36, ES patients showed less GM volume loss compared with DS patients.

- The results of the 3-year OL extension phase of the GALA study support the benefit of GA40 sustained beyond that reported in the PC phase of the trial.

- Relapse-related efficacy seen in GALA for GA40 was generally similar to that seen in previous studies with GA20, in which reductions in ARR were 29%– 33%

- Overall, there were low rates of disability progression events; however, patients with early initiation of GA40 showed a trend toward a delayed progression to 6-month confirmed EDSS 4

- The small number of GdE T1 lesions and new or enlarging T2 lesions at Months 6 and 12 observed in patients treated with GA40 during the PC phase was sustained throughout the OL phase to Month 36.

- In line with this finding, patients who initiated GA40 treatment earlier showed a trend toward less whole-brain volume loss than patients in the DS group, albeit not significantly, except for a trend between Months 12 and 36

- These findings are in agreement with the results from a previous study that showed that GA reduced the rate of brain atrophy compared with placebo from Months 9 to 18 and from Months 0 to 18 but not in the period between Months 0 and 9 using the SIENA method

- In summary, treatment with GA40 conferred clinical benefit over 3 years of the GALA study, resulting in sustained low ARR and MRI lesion activity.

- Results from this OL extension of the GALA study further support the safe and effective use of GA40 in the RRMS patient population.

J Neurosci Res. 2014 Dec;92(12):1621-36.

Restoration of axon conduction and motor deficits by therapeutic treatment with glatiramer acetate.

Moore S[1], Khalaj AJ, Patel R, Yoon J, Ichwan D, Hayardeny L, Tiwari-Woodruff SK.

- The underlying multifactorial anti-inflammatory, neuroprotective effect of GA is in the induction of reactive T cells that release immunomodulatory cytokines and neurotrophic factors at the injury site.

- These GA-induced cytokines and growth factors may have a direct effect on axon function.

- Therapeutic treatment with GA significantly decreased clinical scores and improved rotorod motor performance in EAE mice.

- These functional improvements were supported by an increase in myelinated axons and fewer amyloid precursor protein-positive axons in the spinal cords of GA-treated EAE mice.

- Furthermore, therapeutic GA decreased microglia/macrophage and T cell infiltrates and increased oligodendrocyte numbers in both the spinal cord and corpus callosum of EAE mice.

- Finally, GA improved callosal axon conduction and nodal protein organization in EAE.

Value Health. 2015 Nov;18(7):A766.

Adherence to Glatiramer Acetate 40 Mg Versus Oral Disease-Modifying Therapies for Multiple Sclerosis.

Halpern R[1], Wolbeck R[1], Blauer-Peterson C[1], Wu Y[2], Gandhi SK[2].

- To compare adherence to glatiramer acetate 40 mg (GA40) and oral disease modifying therapies (DMTs; fingolimod, teriflunomide, dimethyl fumarate) using a US administrative claims database.

- Patients were ≥ 18 years old, enrolled 6 months pre-index and ≥ 3 months post-index, and diagnosed with MS.

- The final sample was 1,779 patients (232 GA40, 1547 oral DMT), with mean age 45.5 years and 77.9% female.

- The GA40 and oral DMT cohorts had 0.39 versus 1.07 discontinuations/person-year, respectively, for an incidence rate ratio of 2.75 ($p < 0.001$).

- Kaplan-Meier analysis showed that GA40 cohort was more persistent per post-index 90-day interval ($p < 0.001$).

- Mean (standard deviation) MPR and PDC in the GA40 cohort were 0.88 (0.18) and 0.87 (0.20), respectively, versus 0.84 (0.18) and 0.70 (0.30) in the oral DMT cohort (both $p < 0.001$).

- Mean MPR was 0.90 (0.16) in the GA40 cohort with ≤ 210 post-index days versus 0.86 (0.16) for oral DMT ($p < 0.05$); mean MPR was not significantly different between the cohorts with maximum 270 or 330 post-index days.

- Mean PDC was higher in the GA40 cohort in all comparisons (all $p < 0.001$).

- MS patients starting GA40 were more persistent and at least as adherent (similar on MPR and better on PDC) compared with those starting oral DMTs, possibly due to GA40's safety profile and less-frequent dosing schedule.

J Neuroimaging. 2015 Nov-Dec;25(6):989-95.

The Effect of Three Times a Week Glatiramer Acetate on Cerebral T1 Hypointense Lesions in Relapsing-Remitting Multiple Sclerosis.

Zivadinov R[1], Dwyer MG[1], Ramasamy DP[1], Davis MD[2], Steinerman JR[2], Khan O[3].

- Two definitions of T1 hypointense (T1H) lesions can be derived from pre-contrast images: those that may or may not have a corresponding gadolinium-enhancing correlate on post-contrast images (T1H total), and those that are simultaneously non-gadolinium-enhancing on post-contrast scans (T1H non-enhancing).

- To determine the differences in lesion evolution between these two T1H definitions, we examined the effect of glatiramer acetate 40 mg/mL three times weekly subcutaneous injection (GA40) on the number of new or enlarging T1H total and T1H non-enhancing lesions in patients with RRMS.

- Among the 1,357 patients with MRI scans performed at either the month 6 or month 12 visit, 883 treated with GA40 developed an adjusted cumulative mean of 1.72 T1H total lesions versus 2.62 in 440 placebo controls ($P < .0001$).

- On T1H non-enhanced scans, GA40-treated patients developed an adjusted cumulative mean of 1.35 T1H non-enhancing lesions versus 1.91 in placebo controls ($P = .0009$).

- GA40 significantly reduced the number of new or enlarging T1H total lesions and T1H non-enhancing lesions compared with placebo.

- Although the treatment effect magnitude was comparable with both definitions, the use of T1H non-enhancing lesions may be more relevant for more uniform standardization in future clinical trials.

Patient Prefer Adherence. 2014 Aug 21;8:1123-34.

Two decades of subcutaneous glatiramer acetate injection: current role of the standard dose, and new high-dose low-frequency glatiramer acetate in relapsing-remitting multiple sclerosis treatment.

Caporro M[1], Disanto G[1], Gobbi C[1], Zecca C[1].

- Glatiramer acetate, a synthetic amino acid polymer analog of myelin basic protein, is one of the first approved drugs for the treatment of RRMS.
- Several clinical trials have shown consistent and sustained efficacy of GA 20 mg sc daily in reducing relapses and new demyelinating lesions on MRI in patients with RRMS, as well as comparable efficacy to high-dose interferon beta.
- Some preclinical and clinical data suggest a neuroprotective role for GA in multiple sclerosis.

- GA is associated with a relatively favorable side-effect profile, and importantly this was confirmed also during long-term use.

- GA is the only MS treatment compound that has gained the US Food and Drug Administration pregnancy category B.

- All these data support its current use as a first-line treatment option for patients with CIS or RRMS.

- More recent data have shown that high-dose GA (ie, 40 mg) given three times weekly is effective, safe, and well tolerated in the treatment of RRMS, prompting the approval of this dosage in the US in early 2014.

- This high-dose, lower-frequency GA might represent a new, more convenient regimen of administration, and this might enhance patients' adherence to the treatment, crucial for optimal disease control.

GA Indications

- RRMS
- Pregnancy
- Concomitant psychiatric disorder
- Concomitant hepatic or hematologic disease
- Concomitant autoimmune disease