# A Bayesian meta-analysis of longitudinal lesion count in multiple sclerosis patients

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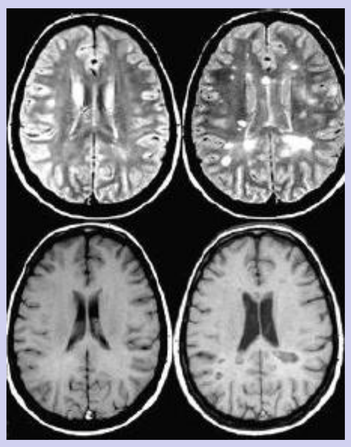


## Introduction and objectives

• The medicinal drugs currently proposed, in US or in EU, as 1st line treatment of relapsing-remitting multiple sclerosis (MS) are the interferon-beta, glatiramer acetate, and fingolimod. In addition, a number of candidate compounds are being developed in this indication.

• With access to literature data and using meta-analysis methodology, it is possible to inform decision-making for the development of a new compound, for instance by comparing new phase 2 efficacy data to the ones publicly available from other compounds.

• Reduction in number of brain MRI lesions is a commonly used measure of therapeutic effect for drugs developed in MS clinical trials, in particular in phase 2.

• The aim of this analysis is to **characterize the time dynamic of lesion counts observed in MS patients treated with various pharmaceutical agents**

## Modeling procedure

• The studied response is the group-level average of new gadolinium-enhanced lesions counted per scan.

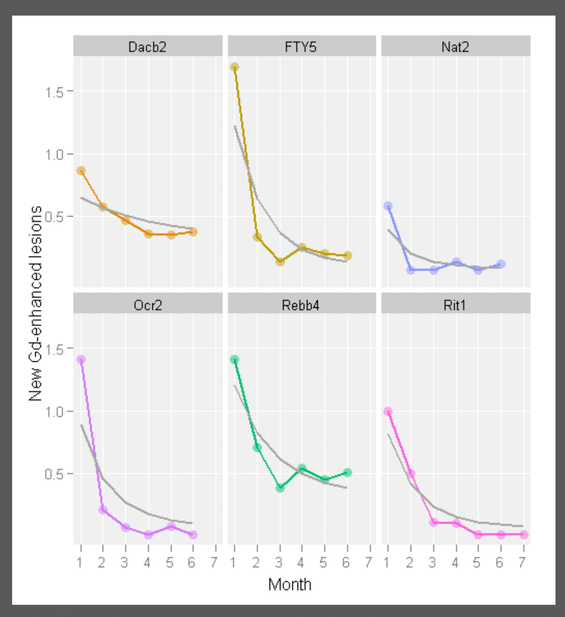
• The number of gadolinium-enhanced lesions at baseline (*T1B*), a well-known covariate to account for when analyzing reduction of lesion count was introduced in our models.

• PLACEBO data were available from 13 different trials. Various linear models were tested to fit these data.

• Based on the data display, Hill-$E_{max}$, $E_{max}$, bi-exponential and mono-exponential models were test to fit the data collected in patients treated with ACTIVE compounds. The model finally retained for active treatments was a mono-exponential model (**Figures 2-3**)

## ACTIVE

**Figure 2: A subset a group-level new-Gd enhanced lesion count (*nGd*) over time**




Note: One dot per observed mean by treatment group and assessment time point; Grey represents the predicted values.

- The *nGd* lesion count in MS patients treated with an active compound generally decreased over time to reach asymptotically a treatment-specific floor.

- This trend was adequately captured using a mono-exponential model:

$$Y_{jk} \sim N\left(\mu_{jk}, \frac{\sigma^2_{res}}{\sqrt{N_j}}\right)$$
$$\mu_{jk} = Asym_j + E_{0j} \times \exp\left(-\lambda_j \times Month_k\right)$$
$$E_{0j} = \left(\alpha \times T1B_j\right)$$

where *j* is the treatment group index, *k* is the time index; *Asym* is the asymptotically lowest lesion count; a non-informative uniform prior distribution was associated with the $\alpha$ parameter

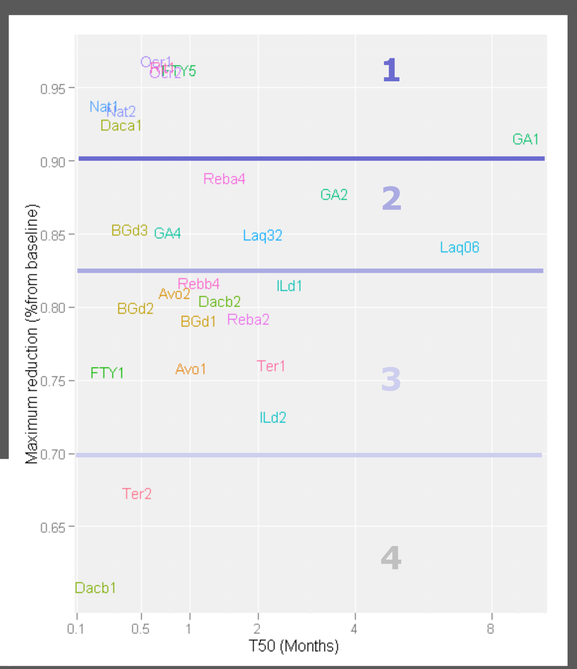
- A *subset* of observed and predicted time profiles are presented in **Figure 2**.

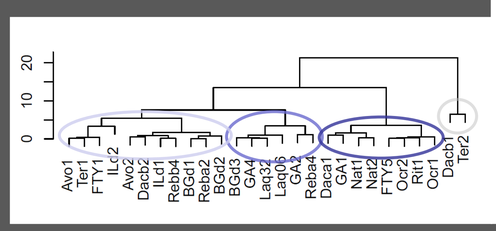
- From this saturated model, the maximum reduction (% from baseline) in lesion count, and the time to reach 50% of the full effect (*T50*) (**Figure 3**) were derived.

- A cluster analysis allowed to identify four (4) major categories of compounds according to their potency:

**1**: Very-high efficacy: mAb, FTY high dose;
**2**: High efficacy: High-dose of BG-12, GA, IFNβ-1a, laquinimod;
**3**: Moderate efficacy: Medium-dose of IFNβ-1a, BG-12, FTY, IL12/23;
**4**: Low efficacy: Teriflunomide.

**Figure 3: Time of onset and potency of 12 MS compounds in reducing *nGd***




Legend: Avo=IFNβ-1a 30 µg IM qw; BG=BG-12 (d1) 120 mg qd, (d2) 120 mg tid, (d3) 240 mg tid; Dac=Daclizumab (a1) 1 mg/kg IV q4w+IFN, (b1) 1 mg/kg SC q4w+IFN, (b2) 2 mg/kg SC q2w+IFN; FTY=Fingolimod (1) 1.25 mg po qd, (5) 5 mg po qd; GA=Glatiramer acetate (1) 20 mg SC qd. (2) 20 mg SC qd, (4) 40 mg SC qd; IL=IL12/23 (d1) ABT-874 200 mg IV eow, (d2) ABT 200 mg IV qw; Laq=Laquinimod (32) 0.3 mg po qd, (06) 0.6 mg po qd; Nat=Natalizumab (1) 3 mg/kg IV q4w, (2) 6 mg/kg IV q4w; Ocr=Ocrelizumab (1) 0.6 g IV SD, (2) 2 g IV SD; Reb= IFNβ-1a (a2) 22 µg SC tiw, (a4) 44 µg SC tiw, (b4) 44 µg SC tiw; Rit=Rituximab 1 g IV day1, day 15; Ter=Teriflunomide (1) 7 mg po qd, (2) 14 mg po qd.

## Conclusion

• Despite the lack of homogeneity in reported endpoints in MS (**Figure 1**), a meta-analysis of longitudinal brain MRI lesion count in MS patients could be run using data from 16 clinical trials.

• Depending on the amplitude of reduction in lesion counts, 4 categories of compounds were identified (**Figure 3**):

- very high efficacy: x-umab and fingolimod high-dose,
- high efficacy: high-doses of BG-12, GA, IFNβ-1a, laquinimod,
- moderate efficacy: Medium-dose of IFNβ-1a, BG-12, FTY, IL12/23,
- low efficacy: Teriflunomide.

• This type of analysis offers a framework to discuss risks and opportunities in developing a new drugs, in regards to the existing competition.

## Material

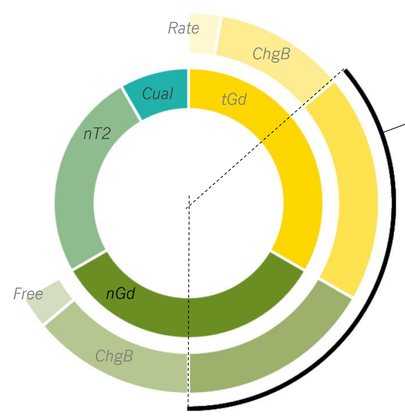
• The scope of screened literature was: randomized, controlled clinical trials, published in scientific journals and MS congresses, and reporting results on the efficacy of disease modifying treatments in MS patients in the form of brain MRI lesion counts.

• The literature database is composed of 56 relevant references, representing a total of 40 unique trials.

• Due to the large diversity in MRI endpoints, expression of the endpoints and frequency of scanning, only 16 unique trials, representing 40 treatment arms, could be retained for the modeling exercise (**Figure 1**).

• Investigated compounds: IFNα-2a, IFNβ-1a, natalizumab, glatiramer acetate, laquinimod, rituximab, IL12/23, fingolimod, BG-12, teriflunomide, daclizumab, and ocrelizumab.

**Figure 1: Articles by *type* of lesion (inner ring) and *expression* of the endpoint (outer)**




Retained in the meta-analysis:
• Longi.means of total or new Gd-enhanced lesion
• 40 treatment arms, 13 of which are placebo
• 3210 patients (2344 active+866 placebo)

TYPE: (*tGd*) total Gd-enhanced lesions; (*nGd*) new Gd-enhanced lesions; (*nT2*) new or enlarging T2 lesions; (*Cual*) Combined unique active lesions.

EXPRESSION: (*Rate*) average rate; (*ChgB*) change from baseline; (*Longi*) longitudinal mean; (*Free*) percentage of lesion free patients.

## PLACEBO

- The time trend observed for *nGd* lesion count in placebo MS patients looked flat; This trend was adequately characterized by a Bayesian longitudinal linear model.

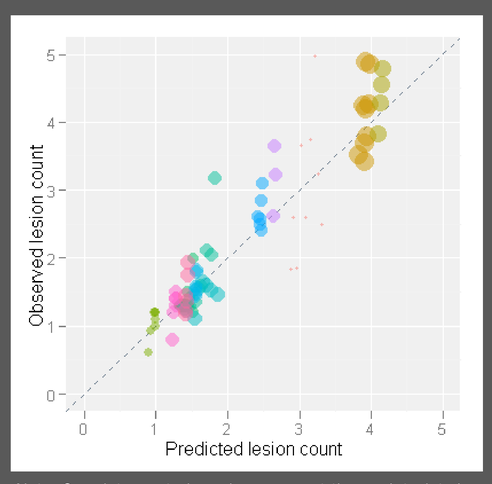
- The between- and within-study variability were estimated using the below model; the between study variability was found to be much higher than the within-study variability.

$$Y_{jk} \sim N\left(\mu_{jk}, \sigma^2_{res}\right)$$
$$\mu_{jk} = \beta_{jk} + \alpha \times T1B_j$$
$$\beta_{j1} \sim N\left(\mu_T, \sigma^2_T\right)$$
$$\beta_{jk} = \beta_{jk-1} + \varepsilon_{jk}$$
$$\varepsilon_{jk} \sim N\left(\mu_{Dev}, \sigma^2_W\right)$$

where *j* is the treatment group index, *k* is the time index; $\sigma_T$ represents the between-trial variability; $\sigma_W$ represents the within trial variability; $\mu_{Dev}$ is the deviation from time slope=0. Non-informative prior distributions were associated with parameters $\alpha$, $\mu_T$, $\sigma_T$, $\mu_{Dev}$, and $\sigma_W$.

- The $\mu_{Dev}$ estimate was found to be equal to -0.01 [95% CI: -0.09, +0.07], *i.e.* absence of time trend; this result contrasts with [2] who stated that placebo MS patients experience a decline of *nGd* over time, based on data from a single trial (PRISMS)

**Figure 4: Obs. *vs.* pred. lesion count (Placebo)**




Note: One dot per study and assessment time point; dot size proportional to N. One color per compound.

## References

[1] Morgan CJ et al. 2010 Multiple Sclerosis, 16(8): 926-34.
[2] Zhao Y et al. 2008 Neurology, 70: 1092-97.

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