Heterogeneous Virtual Multiple Sclerosis Patients for analysis of personalized treatment responses

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Introduction

One of the major challenges in the treatment of Relapsing-remitting Multiple Sclerosis (RRMS) is the diversity and unpredictability of RRMS disease courses. Currently, a wide array of treatment options with different efficacy and safety profiles is available on the market, and development of new therapies is ever ongoing. However, answering the question of the most appropriate drug for a patient, and the most appropriate target population for a new drug, is no easy task. Here, a population of virtual patients (VPs) with RRMS was generated and treated in silico with several different treatment options. The response of the VPs to the treatments was analysed in terms of individual differences in efficacy.

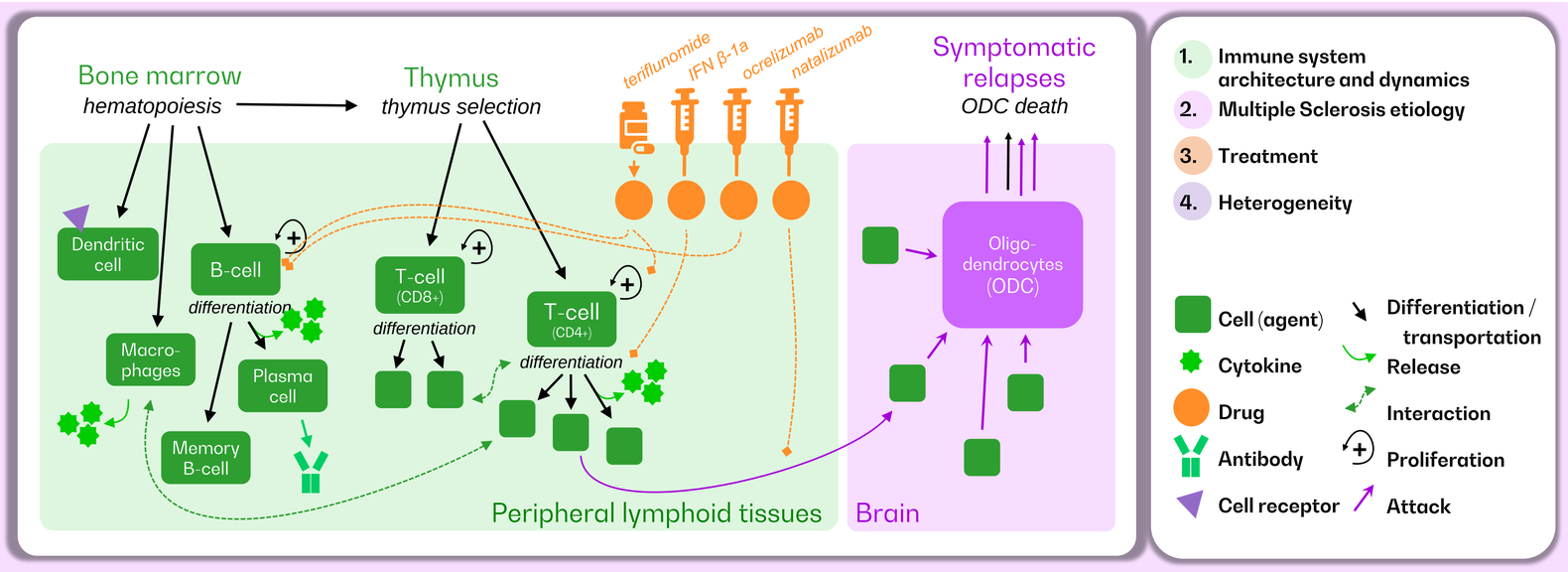
Objectives: To analyse interpersonal efficacy response differences to treatments in RRMS VPs.
Aims: To support personalized treatment in RRMS through characterization of individual patients optimal efficacy profiles.

Methods

VPs were generated with MS TreatSim, a web-based, cloud-based VP and clinical trial simulator available at mstreat.insiliconeuro.com. MS TreatSim VPs are individualized instances of a mechanistic immune system simulator (Figure 1), that has been induced to develop RRMS. The VPs, with active RRMS, were simulated for 260 weeks with four different treatment protocols – no treatment, interferon β-1a, teriflunomide and natalizumab. Efficacy responses were then quantified within each VP to obtain individual analyses of the differences in treatment responses and stratified for further analysis.

Schematic overview of the underlying agent-based model.

The cloud-based simulator utilizes a personalized, validated agent-based immune system simulator. The **immune system** (**1**) forms the basis of the model, incorporating fundamental processes and cell types of both the innate and adaptive immune systems. **Multiple Sclerosis etiology** (**2**) was incorporated by extending the model with an explicit white matter compartment, in which oligodendrocytes are attacked and destroyed by the autoresponsive immune system during active disease. **The four treatment options** (**3**) – interferon β-1a, teriflunomide, natalizumab and ocrelizumab - are each incorporated through their pharmacokinetic characteristics and their mechanism of action. Finally, **heterogeneous virtual Relapsing-remitting Multiple Sclerosis patients** (**4**) are created by mapping demographic and clinical parameters (e.g., age at disease onset, lesion load, immune variability) to underlying mechanistic model parameters, and subsequently selecting the patients of interest with the aid of disease history characteristics.



Workflow of MS TreatSim

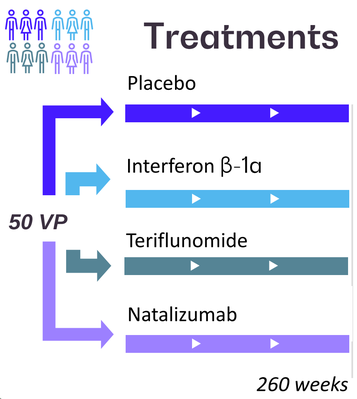
Input

Population

Age distribution: ***default***
Lesion load: ***high***
Oligocl. Bands: ***yes***
Disease length: ***1-5 years***
Activity:
- ***1 relapse in last year, or 2 relapses in last two years***
- ***No relapses in the last month***

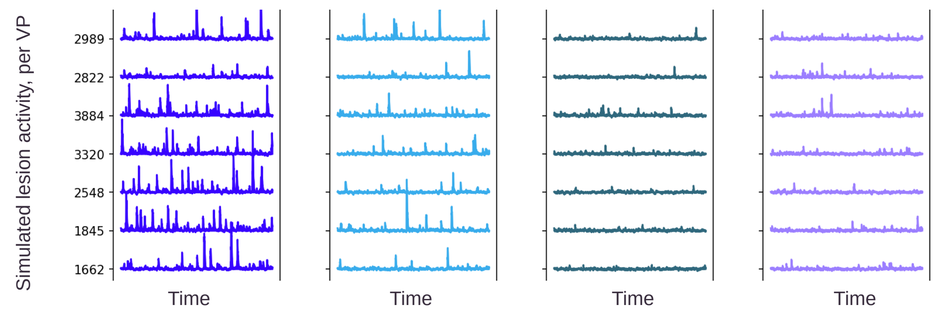
Trial Design

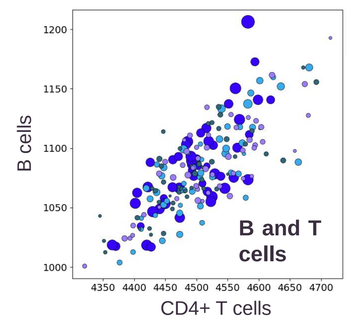
Treatments



Prediction

Outcomes: lesion activity, high level relapse rates, individual immune variables





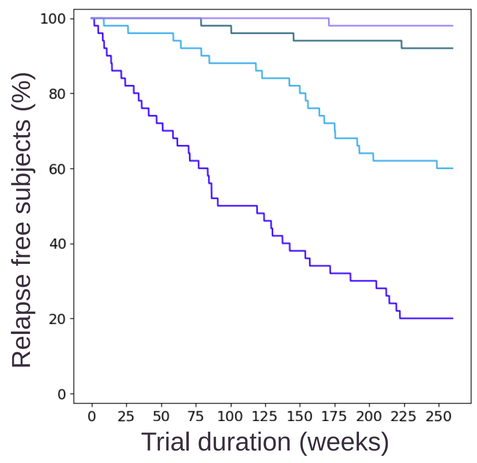
Output

Results

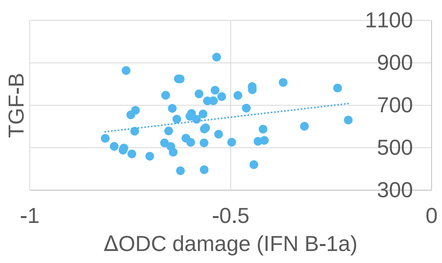
Without treatment, the 50 VPs had an annualized relapse rate of 0.33 ± 0.29 (mean ± SD). With treatment, rates fell to 0.10 or lower and damage to the ODC – a continuous measure of relapse activity and neural damage incorporated in the VP - decreased by medians of 58% (interferon β-1a), 80% (teriflunomide), and 72% (natalizumab), respectively. To investigate inter-individual differences, the responses of VPs to the different treatments were then more closely investigated.

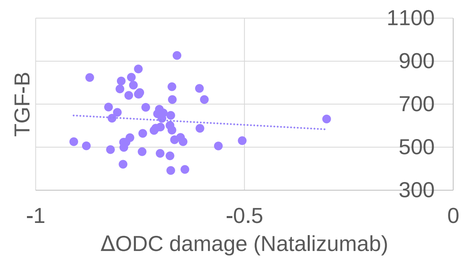
Individual treatment effects correlated more closely between teriflunomide and natalizumab treatment than between interferon β-1a and either teriflunomide or natalizumab.

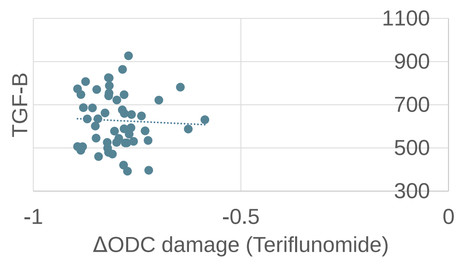
When stratified to high and low responders per treatment, natalizumab and teriflunomide high responders also showed a similar pattern. Good responders to both teriflunomide and natalizumab appeared to have higher baseline TGF-β and higher baseline activated T regulatory cells, whereas good responders to interferon β-1a showed the opposite pattern.



Treatment	Annual relapse rate (mean ± SD)	Treatment effect (ΔODC damage - median)
Placebo	0.33 ± 0.29	n.a.
IFN β-1a	0.10 ± 0.14	-0.57
Teriflunomide	0.01 ± 0.05	-0.80
Natalizumab	0.004 ± 0.03	-0.72







Conclusion

MS TreatSim generates VPs with heterogeneous immune initializations and treatment responses. Analysis of these VPs in terms of not only efficacy, but also leukocyte number-based safety profiles, can help to characterize the optimal efficacy-safety profile for a patient, as well as which patients are the optimal targets for a treatment.

REFERENCES

1) Multiple Sclerosis Treatment Simulator: MS TreatSim – https://mstreat.insiliconeuro.com.
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3) Nicolò C, Sips F, Vaghi C, Baretta A, et al. Accelerating Digitalization in Healthcare with the InSilicoTrials Cloud-Based Platform: Four Use Cases. Ann Biomed Eng 2022; 1–12.