Virtual RRMS patients for clinical trial design: Emulating heterogenous treatment responses

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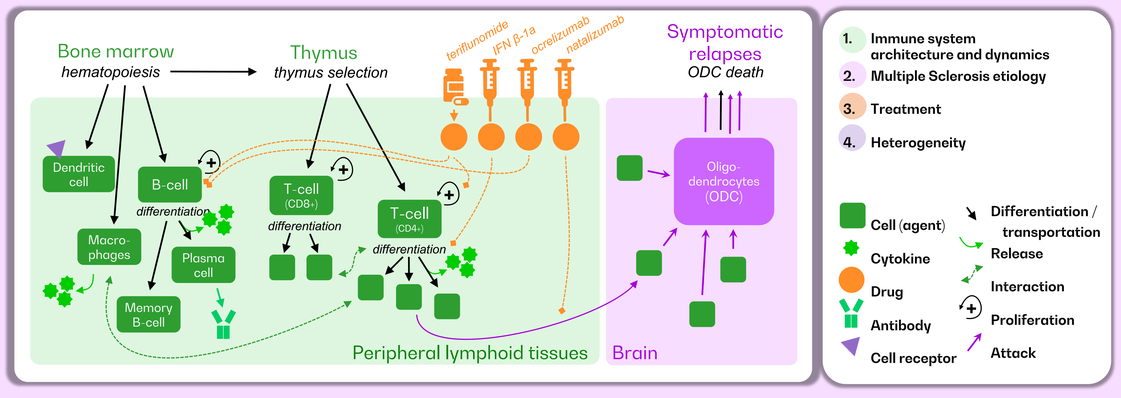
Objective

Clinical trial design in Relapsing-remitting Multiple Sclerosis (RRMS) can be challenging due to the often slow and unpredictable disease progression and great heterogeneity of both disease courses and treatment responses. To support RRMS trial design, we have launched MS TreatSim, a virtual patient (VP) generator that can simulate realistically heterogeneous RRMS disease courses. The simulator is also able to treat its VPs with several commonly prescribed treatment options. Here, we aim to characterize how MS TreatSim's VPs emulate heterogeneity in treatment responses.

Design

50 VPs were generated with MS TreatSim, a cloud-based VP simulator based on an agent-based, individualizable model of RRMS (mstreat.insiliconeuro.com). The 50 VPs were each virtually treated with either interferon β-1a, teriflunomide or natalizumab for 260 weeks. The outcomes for the different treatment protocols were then compared with disease activity in the same VPs without treatment.



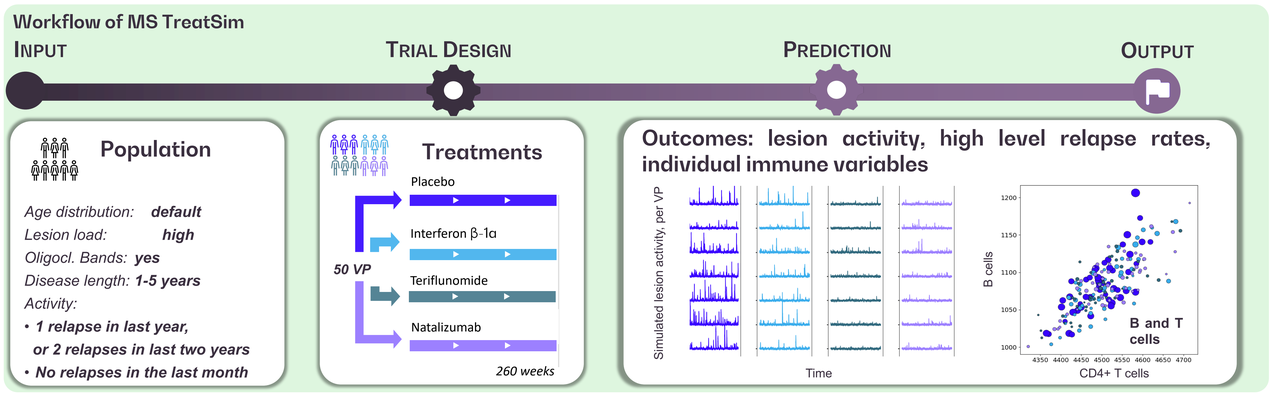
Schematic overview of the agent-based model.

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.

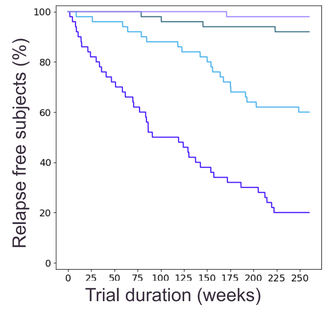
REFERENCES

1) Multiple Sclerosis Treatment Simulator: MS TreatSim – https://mstreat.insiliconeuro.com.
2) Pappalardo F, Russo G, Pennisi M, et al. The Potential of Computational Modeling to Predict Disease Course and Treatment Response in Patients with Relapsing Multiple Sclerosis. Cells 2020;9(3):586.
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.

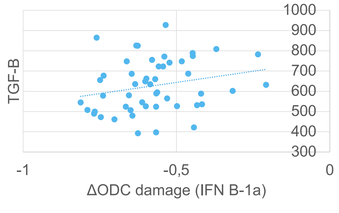
Results

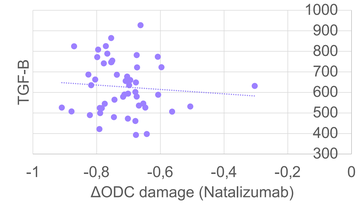


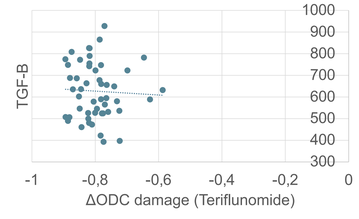
With treatment, relapse rates in the VP population fell from 0.33 ± 0.29 (mean ± SD) to 0.10 or lower, while the continuous disease activity variable – oligodendrocytes damage – was found to decrease by 57% (interferon β-1a), 80% (teriflunomide), and 72% (natalizumab). VPs' heterogeneous treatment responses were further analysed following stratification of VPs by treatment response.



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 disease courses and treatment responses. The VP generator can be used to support trial design by simulating individual VP responses to placebo treatment and several commonly prescribed treatment options, and can be extended to include novel treatment options.