ONLINE SUPPLEMENTARY DATA

Supplementary Table 1. List of medications classified as synthetic or biologic/small molecule

Synthetic	Biologic/Small Molecule
Azathioprine	Abacept (Orencia)
Cyclophosphamide	Adalimumab (Humira)
Hydroxychloroquine (Plaquenil)	Anakinra
Leflunomide (Arava)	Certolizumab (Cimiza)
Methotrexate	Entanercept (Enbrel)
Minocycline	Infliximab
Sulfasalazine	Rituximab
	Tocilizumab
	Tofacitinib

Supplementary Data 1. Detailed methods

We estimated the causal effect of smoking on disease activity at 27 months using longitudinal targeted maximum likelihood estimation (LTMLE), a double robust and semi-parametric efficient approach that allows adjustment for missing measurements and censoring (Petersen et al., 2014). The causal effects of longitudinal exposures can be defined by contrasting the distribution of a counterfactual outcome under different "interventions" to set the values of the exposure variable. When censoring occurs as a result of loss to follow up, counterfactuals for a particular intervention can be generalized to apply to individuals with complete follow-up. We restrict attention to interventions representing "static regimes" (i.e. interventions in which all participants in a population are deterministically assigned the same vector of exposure and censoring decisions; for example, "always smoke and remain under follow up vs. never smoke and remain under follow up). Alternative counterfactuals can also be defined for interventions that assign a treatment or exposure level to each individual at each time point based on the individual's observed past; these "dynamic regimes" were not used in this study and are further described in Petersen et al. (2014).

Longitudinal static and dynamic regimes are often subject to time dependent confounding (Robins et al., 2000), and thus traditional approaches for estimating intervention effects are likely to yield biased estimates. However, the mean counterfactual outcome may still be identified given certain assumptions: sequential randomization and positivity assumptions (Robins and Hernan, 2009). Various estimators can be used to estimate intervention-specific mean counterfactual outcomes, including inverse probability weighted estimators (IPW) (Robins, 1993, 2000a; Hernan et al., 2006), "G-computation" estimators (Robins, 1986; Taubman et al., 2009), augmented-IPW estimators (Robins and Rotniztky 1992; Robins 2000a; Robins 2000b), and targeted maximum likelihood estimation (TMLE) (Rosenblum & van der Laan 2011; Stitelman et al., 2011; van der Laan & Gruber 2012).

Marginal structural models (MSMs) are typically based on parametric models for the counterfactual conditional mean outcome as a function of the choice of intervention and time. Coefficients of both static and dynamic MSMs are frequently estimated using IPW estimators; however, with substantial shortcomings (Petersen et al, 2012). Alternatively, LTMLE, a more efficient and robust approach, are semiparametric, using MSMs as working models because the true shape of the causal dose response curve is typically unknown. Further, LTMLE: 1) is doubly robust against misspecification of the exposure or outcome mechanism alone; 2) provides robustness under strong confounding or rare outcomes as a substitution estimator; and 3) uses machine learning (Super Learner) to build the best weighted combination of estimates from a library of candidate algorithms (van der Laan et al., 2007).

We examined the causal effect of smoking on disease activity as measured by various outcomes at 27 months, while accounting for censoring. Given a class of treatment rules, we can define a true time-dependent causal dose-response curve for some subset, which depends on the scientific question of interest. We can then specify the marginal structural working model to summarize how the counterfactual disease activity score at time *t* (27 months) varies as a function of the assigned exposure. The structural causal model (SCM) representing our knowledge about the time-ordering and relationships between the exposure, covariates, and outcome of interest is:

$$L_0 = f_{L_0}(U_{L_0})$$

$$A1_0 = f_{A1_0}(L_0, U_{A1_0})$$

$$A2_0 = f_{A2_0}(L_0, U_{A2_0})$$

$$L_t = f_{L_t}(A1_{t-1}, A2_{t-1}, L_{t-1}, A1_0,\ A2_0, L_0, U_{L_t})$$

$$A1_t = f_{A1_t}(L_t, A1_{t-1}, A2_{t-1}, L_{t-1}, A1_0, A2_0, L_0, U_{L_t})$$

$$A2_t = f_{A2_t}(L_t, A1_{t-1}, A2_{t-1}, L_{t-1}, A1_0, A2_0, L_0, U_{L_t})$$

$$Y \equiv L_9 = f_Y(A1_{t-1}, A2_{t-1}, L_{t-1}, A1_0, A2_0, L_0, U_Y)$$

where the subscripts denote time points (*t*) in 3 month intervals, with baseline = 0 and 27 months = 9; $A1_j$ denotes the exposure of interest (smoking) within time interval *j*; $A2_j$ denotes the patient's presence (i.e. not censored) within time interval *j*; L_j are the vector of time-varying confounders (variables that influence both future exposure and the outcome of interest) within interval *j*; *Y* denotes the outcome of interest (smoking at 27 months), and the *U*s denote unmeasured, independent error variables. The data can now be represented as a sample of independent, identically distributed observations (O=($\overline{A1}$, $\overline{A2}$, $\bar{L}$, Y)), where over-the-bar notation denotes the history of the variable.

Intervention on the exposure of interest (smoking) and a patient's presence at 27 months corresponds to setting $\overline{A1}_t=\overline{a1}_t$ and $\overline{A2}_t=\overline{a2}_t$, respectively. The counterfactual outcome is represented as the value that *Y* would have taken under universal setting in the population of the hypothetical intervention $\bar{A} = \bar{a}$. Our causal parameter was the expected mean difference in the counterfactual disease activity score at 27 months if all patients were smokers at each timepoint ($\overline{a1}$= (1,1,1…1)) vs. non-smokers ($\overline{a1}$= (0,0,0…0)) and were present (i.e. not censored) at 27 months ($\overline{a2}$ = (1,1,1 ...1): $(\mathrm{E}Y_{\bar{a}1=1,\bar{a}2=1} - \mathrm{E}Y_{\bar{a}1=0,\bar{a}2=1})$ (Pearl, 2009).

Because model misspecification is a concern in analyses with numerous variables and potentially complex relationships among them, we utilized Super Learner to minimize the potential of bias due to regression model misspecification, and to maximize precision of the estimates (van der Laan et al, 2007). The library of candidate prediction algorithms we implemented in Super Learner included generalized linear model; generalized linear model with interactions; mean regression; and Bayesian generalized linear model.

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