J Pharmacokinet Pharmacodyn (2014) 41:479–491
DOI 10.1007/s10928-014-9383-z

ORIGINAL PAPER

Complex pattern of interleukin-11-induced inflammation revealed by mathematically modeling the dynamics of C-reactive protein

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Received: 26 March 2014 / Accepted: 6 September 2014 / Published online: 18 September 2014

Abstract Inflammation underlies many diseases and is an undesired effect of several therapy modalities. Biomathematical modeling can help unravel the complex inflammatory processes and the mechanisms triggering their emergence. We developed a model for induction of C-reactive protein (CRP), a clinically reliable marker of inflammation, by interleukin (IL)-11, an approved cytokine for treatment of chemotherapy-induced thrombocytopenia. Due to paucity of information on the mechanisms underlying inflammation-induced CRP dynamics, our model was developed by systematically evaluating several models for their ability to retrieve variable CRP profiles observed in IL-11-treated breast cancer patients. The preliminary semi-mechanistic models were designed by non-linear mixed-effects modeling, and were evaluated by various performance criteria, which test goodness-of-fit, parsimony and uniqueness. The best-performing model, a robust population model with minimal inter-individual variability, uncovers new aspects of inflammation dynamics. It shows that CRP clearance is a nonlinear self-controlled process, indicating an adaptive anti-inflammatory reaction in humans. The model also reveals a dual IL-11 effect on CRP elevation, whereby the drug has not only a potent immediate influence on CRP incline, but also a long-term influence inducing elevated CRP levels for several months. Consistent with this, model simulations suggest that periodic IL-11 therapy may result in prolonged low-grade (chronic) inflammation post treatment. Future application of the model can therefore help design improved IL-11 regimens with minimized long-term CRP toxicity. Our study illuminates the dynamics of inflammation and its control, and provides a prototype for progressive modeling of complex biological processes in the medical realm and beyond.

Keywords CRP · Non-linear mixed-effects model · Acute inflammation · Chronic inflammation · Akaike information criterion · Model parsimony

Introduction

Inflammation is a hallmark of several pathologies, among which are infectious diseases, autoimmune disorders, atherosclerosis and cancer [1–3]. Inflammation is also a side effect of several drugs, particularly immune-based therapeutics and agents targeting the immune system [4–6]. Inflammatory processes are extremely intricate, being regulated through multiple molecular and cellular pathways in a dynamic nonlinear network of feedback loops [7]. Due to this complexity, inflammation is difficult to disentangle by traditional experimental approaches. Mathematical models are invaluable in the study of such systems, as they allow better mechanistic understanding and precise quantitative prediction of the involved dynamics [8]. Models put forward over the years have described acute and chronic inflammation in different settings (e.g. [7, 9–13]). Still, mathematical systems for inflammation with translational relevance for clinical practice are scarce [7].

A particular case in which inflammation presents in the clinic is that of interleukin (IL)-11 therapy. This pleiotropic immunomodulatory cytokine has a central role in stimulating

Electronic supplementary material The online version of this article (doi:10.1007/s10928-014-9383-z) contains supplementary material, which is available to authorized users.

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megakaryocytopoiesis and effectively raising platelet levels, and is the only thrombopoiesis-inducing factor approved by the Food and Drug Administration (FDA) for chemotherapy-induced thrombocytopenia in solid cancers [14–16]. However, IL-11 holds a multifaceted side effect profile (including fluid retention-associated toxicities) [17–19], preventing the drug from being integrated into standard of care [20]. One critical adverse event of IL-11 treatment, documented in various trials in which the drug has been tested, is the rise in the acute-phase factor C-reactive protein (CRP) [17, 21, 22], a sensitive indicator of immediate and general inflammatory processes [23, 24]. CRP is a product of hepatocytes that is routinely measured in the serum of patients [23, 24], and thought to have important prognostic value for developing several pathologies, i.e. diabetes [25], cardiovascular diseases [26–28], and cancer [29–36]. Despite the clinical significance of CRP as one of the reliable detectors of inflammation, the mechanisms underlying its induction under stimuli and return to baseline are still obscure.

In this study, we modelled the effect of IL-11 on inflammation, as reflected in the levels of CRP (to be denoted CRP-inflammation). Due to paucity of mechanistic knowledge about CRP-inflammation dynamics and their regulation, we tackled this problem by a new top-down biomathematical approach we term "multiple modeling". This methodology develops and exhaustively analyzes many plausible semi-mechanistic models for a physiological or pathophysiological process and relating pharmacokinetic (PK)/pharmacodynamic (PD) effects, surfacing a model which best accounts for the biological phenomenon. The produced IL-11 CRP-inflammation model, fit to retrieve CRP profiles observed in IL-11-treated breast cancer patients, suggests that (1) CRP clearance is a self-controlled process, and (2) IL-11 has not only an immediate influence on CRP incline, but also a prominent long-term "memory" effect, reflected by elevated CRP levels that are sustained for several months. Model simulations show that a multi-cycle regimen of IL-11 therapy can further enhance this chronic low grade inflammation to potentially hazardous levels. These findings emphasize the importance of comprehensively analyzing inflammatory processes, and suggest that treatment regimens minimizing inflammation should be better planned, perhaps on a modeling basis.

Methods

Clinical data

Datasets for evaluating the parameters of the model were derived from published clinical studies on IL-11. Data for evaluating PK parameters of IL-11 administration were obtained from a study in 12 healthy male volunteers, measuring drug concentrations in blood following single subcutaneous (s.c.) delivery [37]. For evaluating PD parameters of CRP inflammation induced by IL-11, data were derived from a study in 12 breast cancer patients receiving daily s.c. injections of IL-11 for a period of 2 weeks prior to receiving chemotherapy [17]. The latter data consisted of averaged CRP dynamics measured individually in four dosage groups (10, 25, 50, and 75 μg/kg).

Modeling approach and model selection strategy

A multiple-modeling approach was employed, due to lack of biological information about the mechanism and its influence by IL-11. Several different semi-mechanistic models were designed, evaluated and compared for their ability to retrieve the IL-11-affected CRP dynamics in the clinical dataset from breast cancer patients. The different inflammation models were implemented on a non-linear mixed-effect modeling (NLMEM) platform, Monolix (Lixoft). Preliminary models and their parameterizations are elaborated below.

In all CRP-inflammation models, the PK of IL-11 was configured as a 2-compartment ODE system (as predesigned and selected from an array of possible formulations; see Supplementary Material section A for the full PK modeling process). This PK model was implemented here under the assumption that there are no significant differences in IL-11 PK between individuals with different gender or disease state, as none have been reported hitherto.

To identify the best CRP-inflammation model, the different preliminary models were compared in a methodical manner. This was done primarily using negative log-likelihood (nLL) values of the models, indicative of the goodness-of-fit to data, and by the Akaike information criterion (AIC) values of the models, indicating the trade-off between the fitness and parsimony. AIC is employed for models in which parameters are smoothly transformed from multivariate normal distribution [38–40]. Low nLL and AIC models were thus considered superior. Differences in AIC between two compared models were assumed to be significant if the p values of the AIC (estimated assuming normal AIC distribution with standard errors) were <0.025. Other criteria exercised for selection of the superior models were low relative standard errors (RSE) of parameter estimates and low condition numbers (CN), indicative of model uniqueness and minimal over-fitting (see "Parameter estimation" section).

Parameter estimation

Procedure

In each preliminary model, parameters were evaluated through the stochastic approximation expectation

maximization (SAEM) algorithm combined with the Monte-Carlo Markov Chain (MCMC) procedure [41–46]. Inter-individual variability (IIV) assumptions for parameters differed between model variants. In the case of an IIV assumption, those parameters were assumed log-normally distributed, and for each such parameter x, an additional parameter ω_x described the standard deviation of the random effect. Since the data for modeling reflected average values of CRP in four dosage groups, with 3 patients in each group [17], all IIV parameters were corrected accordingly: As inferred from the elementary probability theory, the average of K equally-distributed independent normal random variables is itself a random variable, with the same average and a standard deviation equal to

$$\omega_K = \sqrt{\sum_{i=1}^{K} \frac{\omega_x^2}{K}} \quad (1)$$

Thus, for K patients in the averaged groups, the IIV of averaged data is K-times less than that of non-averaged data. The resulting IIV and residual error parameters for the group of averaged subjects were transformed in the reverse direction according to Eq. (1), in order to obtain the respective parameters relevant to the original (non-averaged) population.

RSE of parameter estimates were routinely scrutinized for evaluating uniqueness of solutions of the parameter evaluation process, CN values were examined for degree of correlation of the estimated parameters and for minimizing redundancy and over-fitting of parameters [47, 48]. In some model variants, certain parameters were separately estimated (as they were difficult to identify via the above procedure); estimation steps for these parameters are listed in Supplementary Material section B.

Parameter correlation and parsimony

To minimize the correlations between parameters in a given model, parameters were redefined as follows: when observing high CN values (reflecting two correlated parameters, X and Y), Y was substituted by Z·X; In several cases this led estimates of parameters X and Z to be less correlated than the estimates of X and Y. Similarly, if X and Y were negatively correlated, Y was defined as X/Z. In each case, these transformations were evaluated empirically and re-applied in the model. To enhance parsimony of a given model, two parameters X and Y were set as X = Y.

Error model

All evaluated models assumed a constant error model for the residual error, to (1) precisely estimate the reported high CRP values during treatment, which could significantly influence the patient's toxicity profile, and (2) prevent overestimation of fluctuations in baseline CRP level likely unrelated to IL-11 treatment [49]. The constant random error model was assumed near $1/\sqrt{3}$ mg/dl for the averaged population.

IL-11-induced CRP-inflammation model

Model formulation

We first focused on describing regulation of CRP levels, assuming that they are directly proportional to the state of inflammation [23, 30]. We further assumed that under stimulation (i.e. induced by a drug), the normally low CRP levels can rise by 10–1000-fold [30]. With a short half-life for this protein [23, 30], this allows for the quasi-steady-state assumption that normal CRP synthesis and clearance processes are much faster than inflammation dynamics. Under this assumption, CRP clearance may be constant, or alternatively up-regulated by a positive feedback mechanism, e.g. self-induced toward clearance.

Although the process of cancer progression itself may induce alterations in CRP dynamics (i.e. raise CRP baseline, etc. [30]), we made the assumption that the latter effect is negligible in our system, considering that it occurs on a significantly slower time frame (months-years) as compared to IL-11-inflicted CRP changes. Hence, IL-11 is the only source for CRP stimulation in our model. The PD effect of IL-11 is reflected in the clinical CRP profiles throughout and post therapy [17], and can be described by the following features: (i) IL-11 induces an immediate rise in CRP [17, 21] in a linear dose-dependent manner; (ii) CRP levels begin to decline during the IL-11 treatment period, already from day 5 [17], implying self-induced clearance of CRP, occurring on a slower time scale and resulting in a delay, such as might be seen with downstream gene effects; (iii) CRP levels post IL-11 treatment (days 19–26) do not drop back to the normal baseline, but rather remain at a slightly higher residual level [17], suggestive of a possible long-term "memory" effect. This effect appears to be a direct result of IL-11 stimulation, given that the post-treatment residual CRP levels were higher with larger IL-11 doses. The actual time of CRP return to baseline is unclear (not reported in [17], likely due to the limited time frame of the clinical study).

Theoretically, these assumptions can be encompassed in several alternative models. In order to check their plausibility, a number of model types describing the effect of IL-11 on CRP were examined. In the simplest case, where CRP clearance is assumed constant (type A model), the following 2-compartment system of equations is given:

$$\begin{aligned}\frac{dM}{dt} &= p_0 \cdot I - d \cdot M \\ \frac{dC}{dt} &= p_1 \cdot I^{\gamma_1} + p_2 \cdot M^{\gamma_2} - k \cdot (C - C_0),\end{aligned} \tag{2}$$

with the initial conditions $C(0) = C_0$ and $M(0) = 0$.

Here, M is an intermediate memory variable, which is formed at rate p_0, directly depending on IL-11 concentration, I, and is eliminated at rate d. C denotes plasma CRP level, on which serum IL-11 levels (I) induce a direct effect at rate p_1, or a memory effect with coefficient p_2; the negative feedback process, in the third term of the equation for CRP, exponentially restores CRP levels back to the normal baseline level (C_0), with coefficient k. To allow for direct or memory effects of IL-11 to be either linear or nonlinear, they are described by a power dependency, via coefficients γ_1 and γ_2 respectively. A linear effect is given by $\gamma = 1$, a self-induced effect by $\gamma > 1$, and a saturated effect by $\gamma < 1$. The IL-11 concentrations in plasma are derived from a preselected PK model for the drug, constructed separately (see Supplementary Material section A).

In a more complex model (type B model), CRP clearance is regulated by positive linear feedback. This gives the following redefinition of the system:

$$\begin{aligned}\frac{dM}{dt} &= p_0 \cdot I - d \cdot M \\ \frac{dC}{dt} &= p_1 \cdot I^{\gamma_1} + p_2 \cdot M^{\gamma_2} - R \cdot (C - C_0) \\ \frac{dR}{dt} &= a_1 \cdot (C - C_0) - a_2 \cdot (R - R_0),\end{aligned} \tag{3}$$

with the initial conditions $C(0) = C_0$, $M(0) = 0$ and $R(0) = 0$.

The rate at which CRP returns back to its basic level is a variable, R, which is itself positively (linearly) regulated by the CRP concentration. Parameter R_0 is the natural rate of CRP clearance; parameter a_1 is the rate of the induction of CRP self-induced clearance process, and a_2 describes the relaxation rate of this process.

Alternatively, the positive feedback regulation on CRP clearance may be described as non-linear, yielding a type C model. In this model type, variable R rises in a saturated manner, as is given by:

$$\frac{dR}{dt} = a_1 \cdot \frac{C - C_0}{h + C - C_0} - a_2 \cdot (R - R_0), \tag{4}$$

with the initial condition $R(0) = 0$.

Parameter h denotes the deviation of CRP from its basic level, which corresponds to the half of maximal increase rate of R. To avoid parameter correlations (as described in "Methods" section), h was redefined as

$$h = h_1 \cdot a_1, \tag{5}$$

where h_1 and a_1 are estimated.

In all three model types, the equation for M, the intermediate memory variable, is the same (as specified in Eq. 2). Since M is a hypothetical variable that cannot be measured, parameter p_0 is redundant and cannot be estimated at present. Thus, for simplicity, we may redefine M so that it is normalized:

$$\overline{M} = \frac{M}{p_0}$$

This gives a simplified system without parameter $p0$:

$$\begin{aligned}\frac{d\overline{M}}{dt} &= I_2 - d \cdot \overline{M} \\ \frac{dC}{dt} &= p_1 \cdot I_2^{\gamma_1} + \overline{p}_2 \cdot \overline{M}^{\gamma_2} - R \cdot (C - C_0),\end{aligned} \tag{6}$$

where

$$\overline{p}_2 = p_2 \cdot p_0^{\gamma}.$$

Since M is a hidden variable, p_0 is set at the value of 1 for all cases, with no loss of generality.

For each of these three CRP model types, several model variants were simulated, where the variants differed in (i) IIV assumptions on system parameters (h, a_1, a_2, k) or IL-11-effects parameters (p_1, p_2, d, γ_1, γ_2); (ii) absence or presence of the IL-11 memory effect (i.e. setting p_2 at zero or at a positive value); (iii) linearity, self-induction, or saturation of the IL-11 effects (controlled by values of γ_1 and γ_2); (iv) parsimony-motivated assumptions, i.e. setting $\gamma_1 = \gamma_2$, $a_1 = a_2$, etc. (as defined in "Methods" section). The performance of all these models was evaluated by the same criteria (nLL, AIC, RSE and CN). Table 1 displays the collection of models analyzed and their characteristics (see also full description in the Supplementary Material, section C, Table S4). The comparison between the many models, as described in the next section, allowed us to pinpoint the best-performing inflammation model, thus suggesting new mechanistic insights into the processes of systemic CRP regulation and on the influence of IL-11 on CRP-inflammation.

Model selection

CRP clearance by self-induction

Comparison of the three preliminary model types A, B and C showed that an assumption of self-induced positive feedback within CRP clearance improved the model's fit to data: AIC values in type B models (models 7–8; Table 1) and type C models (models 9–35; S4) applying the assumption of self-induced clearance were collectively lower than type A models (models 1–6; S4) which assumed constant clearance (Fig. 1a). Overall CN scores were also lower in type B and C models (Fig. 1a). This positive feedback for CRP clearance is likely

Table 1 Analysis of preliminary IL-11-induced CRP-inflammation models

M	Type	IIV parameters	Parameter parsimony assumption	nLL	AIC	CN
1	A	–	$\gamma_2 = \gamma_1$	125.58	139.58	490
2	A	–	$\gamma_2 \neq \gamma_1$	125.77	141.77	470
3	A	–	$\gamma_2 = \gamma_1 = 1$	126.80	138.8	660
4	A	–	$\gamma_2 = \gamma_1 = 1$	127.48	141.48	1000
5	A	C_0	$\gamma_2 = \gamma_1$	124.56	140.56	530
6	A	–	$\gamma_2 = \gamma_1$	125.62	139.62	NaN
7	B	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	87.44	101.44	350
8	B	–	$\gamma_2 = \gamma_1$, $a_1 = a_2$	94.21	110.21	1400
9	C	–	$\gamma_2 \neq \gamma_1$, $a_1 \neq a_2$	78.81	100.81	1500
10	C	–	$\gamma_2 \neq \gamma_1$, $a_1 \neq a_2$	78.90	100.90	NaN
11	C	C_0	$\gamma_2 \neq \gamma_1$, $a_1 \neq a_2$	79.13	103.13	860
12	C	γ_1,γ_2, a_1, a_2, k, h_1, p_1, p_2	$\gamma_2 \neq \gamma_1$, $a_1 \neq a_2$	87.23	129.23	1200
13	C	γ_1	$\gamma_2 \neq \gamma_1$, $a_1 \neq a_2$	79.04	103.04	NaN
14	C	–	$\gamma_2 \neq \gamma_1$, $a_1 = a_2$	82.09	102.09	260
15	C	–	$\gamma_2 \neq \gamma_1 = 1$, $a_1 = a_2$	82.46	100.46	36
16	C	–	$1 = \gamma_2 \neq \gamma_1$, $a_1 = a_2$.	81.97	99.97	130
17	C	–	$\gamma_2 = \gamma_1$, $a_1 \neq a_2$	79.86	99.86	NaN
18	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 \neq a_2$	81.76	99.76	120
19	C	–	$\gamma_2 = \gamma_1$, $a_1 \neq a_2$	79.87	101.87	940
20	C	–	$\gamma_2 = \gamma_1$, $a_1 \neq a_2$	79.98	99.98	730
21	C	–	$\gamma_2 = \gamma_1$, $a_1 = a_2$	83.83	99.83	52
22[a]	C	C_0	$a_1 = a_2$	103.50	121.5	300
23[a]	C	C_0	$\gamma_1 = 1$, $a_1 = a_2$	103.42	119.42	33
24[a]	C	–	$a_1 = a_2$	102.98	118.98	NaN
25	C	C_0	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.69	101.69	55
26	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.03	99.03	NaN
27	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.12	99.12	23
28	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.20	99.2	23
29	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.36	99.36	23
30	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.55	99.55	25
31	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.15	99.15	23
32	C	–	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	85.16	101.16	27
33	C	–	$\gamma_2 = \gamma_1$, $a_1 = a_2$	82.33	100.33	160
34	C	a_1,k, h_1,p_1,p_2	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	84.73	110.73	20
35	C	p_2	$\gamma_2 = \gamma_1 = 1$, $a_1 = a_2$	83.98	101.98	19

Summary of the assumptions underlying 35 preliminary models for CRP-inflammation and their evaluation for retrieving CRP profiles in breast cancer patients; see further explanation in "Methods"; full Table appears in section C of Supplementary Material (Table S4)

M preliminary model, *IIV* inter-individual variability; *CN* condition number, *nLL* negative log-likelihood, *AIC* Akaike information criterion, *NaN* unidentified

[a] Models that assume one PD effect by setting $p_2 = 0$ (i.e. models accounting for solely the direct IL-11 effect, without the long-term memory effect)

non-linear (saturated), as type C models were superior to type B models (that assumed linear self-clearance): Type C models compared to their B model equivalents (i.e. models with similar IIV assumptions and parameter parsimony, etc.) showed lower AIC and CN values (Fig. 1b). This finding implies that following a surge in CRP, it is cleared in a dynamic non-linear manner involving self-induction of natural elimination mechanisms.

Parsimony in model parameters

Parsimonious parameterization within the type C model group (see "Methods" section) improved the performance

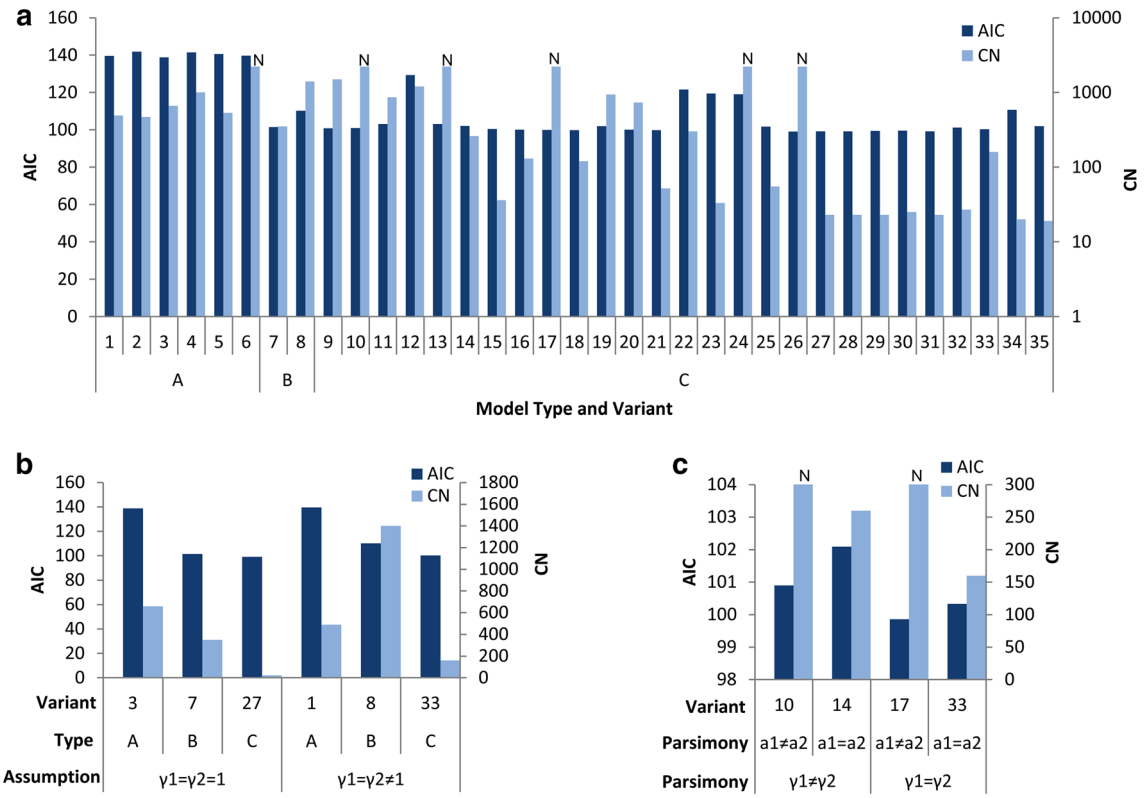

Fig. 1 Performance scores for preliminary models with different assumptions about IL-11-induced CRP-inflammation. **a** Final scores of model evaluation criteria (AIC and CN values) for the collection of analyzed models belonging to three IL-11-induced inflammation model types A–C (differing in the CRP clearance being constant, self-induced linear, or self-induced saturated, respectively); **b** AIC and CN values for models with comparable parsimony assumptions, but belonging to different model types A–C; **c** AIC and CN values for type C models with different parsimony assumptions. All values are a result of fitting the model to CRP profiles of IL-11-treated breast cancer patients (derived from a clinical study; [17]). Columns marked with *N* indicate unidentified CN values

substantially for certain models. For example, setting the induction and relaxation rates of the self-induced CRP clearance process at the same value, i.e. $a_1 = a_2$, made CN values identifiable (model 14 vs. model 10; Fig. 1c). This suggests that CRP regulation is induced and relaxed at the same potency. Similarly, setting the same power for both the direct and long-term IL-11 effects (i.e. $\gamma_1 = \gamma_2$) slightly improved the model's AIC (model 17 vs. model 10; Fig. 1c), albeit its CN was still unidentifiable. Applying both parsimony assumptions ($\gamma_1 = \gamma_2$ and $a_1 = a_2$) together gave the best result, as observed in model 33 (with a lower AIC and an identifiable CN; Fig. 1c). In view of this, we conclude that both direct and long-term IL-11 influences on CRP elevation are of comparable potency.

Linearity in memory effects of IL-11

For elucidating the nature of the direct and long-term memory effects of IL-11, we examined models differing in values for the power parameters of these processes ($\gamma_1 = \gamma_2$). Introducing linearity to at least one of these coefficients in models assuming $a_1 = a_2$ decreased the AIC and CN, as shown in models 15 and 16 ($\gamma_1 = 1$ or $\gamma_2 = 1$) versus model 14 (Fig. 2a). Interestingly, setting both effects as linear ($\gamma_1 = \gamma_2 = 1$) further improved the model, as seen in model 27. A similar observation was noted for models assuming a_1 unequal to a_2: model 18 had an identifiable CN as compared to model 17 (Fig. 2a). This confirmed that IL-11 affects the CRP rise in a linear manner.

Long-term IL-11-induced CRP (memory effect)

We next examined the significance of including the long-range memory effect of IL-11 on CRP elevation in the model. Models consisting of only the direct IL-11 effect (i.e. models 23–24 in which parameter $p_2 = 0$) had poorer performance scores, as shown by higher AIC and nLL values than those of parallel models with both effects (positive p_2; models 14 and 27; Fig. 2b). This confirmed that the memory effect causing prolonged inflammation is

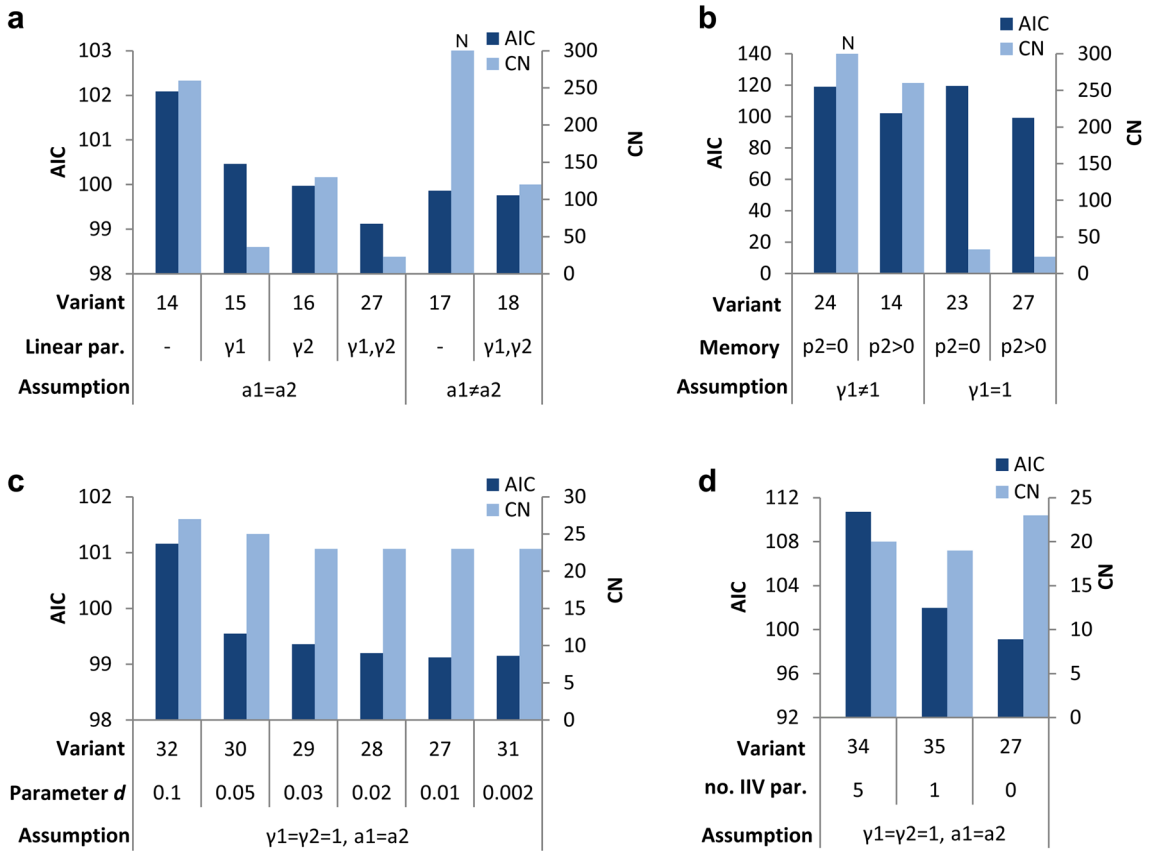

Fig. 2 Performance score for type C models varying in assumptions about IL-11-induced inflammation. Final model evaluation criteria (AIC and CN values) for (**a**) type C models differing in linearity/non-linearity of direct and/or long-term IL-11 effects; **b** type C models differing in inclusion of the long-term IL-11 effect; **c** type C models differing in the value for parameter *d*, the decay rate of the long-term IL-11 effect; **d** type C models differing in number of parameters with IIV assumptions. All values are a result of fitting the model to CRP profiles of IL-11-treated breast cancer patients (derived from a clinical study varying in; [17]). Columns marked with *N* indicate unidentified CN values

an essential aspect of the influence of IL-11 on CRP regulation.

To study the duration of the long-term effect of IL-11 more carefully, in selected models we modified the degradation rate of the memory effect (parameter *d*). In line with the biologically relevant range of *d* (i.e. 0.002–0.1 day^{-1}; see Supplementary Material section B), variants of the best type C model (with parsimony and linear IL-11 effects as above) with different *d* values in this range were evaluated. Models with $d \leq 0.02$ were most acceptable, as evident by their low AICs and CNs, whereas models with higher *d* values led to poor performance criteria (Fig. 2c). We concluded that the IL-11-induced memory effect on CRP carries on for at least 1 month following dosing.

Inter-individual variability

We also tested whether assumptions of IIV would improve model performance. Compared to the best-fit model hitherto (model 27), model 34 that sets IIV for parameters a_1, k, h_1, p_1, and p_2 was scored with a worse AIC (Fig. 2d), although the CN of this variant was slightly lower. Even assuming one parameter with IIV (i.e. model 35) still resulted in a higher AIC than model 27, and was rejected (Fig. 2d). This indicates that IIV is an insignificant factor in the IL-11/CRP system, where all model parameters can essentially be population-based and do not need to be individualized.

The selected model

The above comparative analysis suggests that IL-11-induced CRP-inflammation has the following properties: (1) CRP clearance is a saturated, self-controlled process; (2) the impact of IL-11 on CRP dynamics consists of a short-term direct effect, but also a long-term effect lasting for at least 1 month post therapy; (3) both IL-11-induced effects on CRP can be described by a linear relation; and (4) in IL-11-mediated CRP-inflammation, variability

between patients is not an essential factor. These properties are described by model 27, which is the best performing model (schemed in Fig. 3). The fit of model 27 to the CRP profiles under each of the four tested IL-11 doses is shown in Fig. 4a. The fit was unbiased and the linear regression curves approached the identity line (Fig. 4b). Models 28 and 31 (distinguished from variant 27 only in the duration of the long-term effect of IL-11) reached comparable performance (see above), and were therefore also acceptable. Parameter values and standard errors for these models appear in Table 2. Of note, the calculated residual constant error for these models was 1.62 mg/dl, a value that is in line with the CRP detection error in the clinic.

Model simulation

Since the selected IL-11 inflammation model points to a potentially long-lived CRP incline, we used the model to examine this process. Particularly, we tested the effect of several consecutive cycles of IL-11 therapy on CRP levels. To examine this, the selected model 27, and the comparable models, 28 and 31, were simulated under five 28-days treatment cycles, where daily IL-11 injections (50 or 100 ug/kg) for 2 weeks were followed by a 2-week resting period in each cycle. Simulations were carried out in a deterministic setting, i.e. simulating an average subject using the evaluated population parameters (median values). All three models produced similar dynamics (Fig. 5): High CRP concentrations, predicted during the first cycle, were followed by lower peaks in the subsequent four cycles, likely due to the positive self-induced CRP clearance process. In parallel, a gradual increase in the residual CRP level was noted, and this baseline differed between the models (in line with their diverse values for parameter *d*). Our model therefore predicts that multi-cycle IL-11 therapy would likely not infer a stronger CRP peak than seen after one cycle, yet may contribute to a continuous chronic state of inflammation.

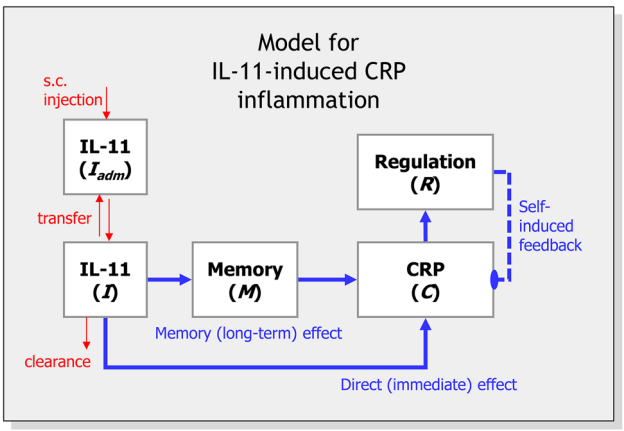

Fig. 3 The selected PK/PD model for IL-11-induced CRP-inflammation. The model (variant 27) is a 5-compartment system, comprised of 2-compartments for IL-11 PK (describing drug levels at the injection site, *Iadm*, and plasma concentration of the drug, *I*), and 3 additional compartments for IL-11 PD effects on CRP (*C*)—the marker for inflammation. The self-regulation of CRP is controlled by component *R*, and the long term effect of IL-11 on CRP is mediated through a memory factor, *M*. PK transfer processes are marked by *thin arrows*; PD effects are marked by *thick arrows* (*solid lined*-stimulating effects; *broken lines*—inhibiting effects)

Discussion

The clinical importance of CRP as a valid risk factor for several diseases has been well established [25–36]. Minor perturbations in this tightly regulated factor are a potential signal of underlying inflammatory processes [23, 24]. Indeed, even low-grade inflammation (defined by CRP levels below 10 mg/L) is thought to be detrimental, increasing the likelihood of disease. For example, CRP is positively related to the development of breast cancer, especially in the early stage [50], and breast cancer patients displaying CRP $>$ 3 mg/L at diagnosis have a 1.7-fold increased risk of death as compared to patients with CRP levels $<$ 1 mg/L at diagnosis [30]. Similarly, clinical practice recommendations for CRP testing in cardiovascular risk assessment regard a uniform CRP level of $>$3 mg/L as a high risk [28]. Given that CRP-inflammation is induced by several biological mediators, i.e. proinflammatory cytokines (IL-11, but also IL-1, IL-6, and IL-17), hormones, and other external stimuli [24], analyzing the contribution of only one externally applied factor, IL-11, to CRP profiles is required for disentangling the intrinsically complex inflammation dynamics. In this context, our present model of IL-11-induced changes in CRP levels in cancer patients can be viewed as a first step in achieving this goal.

The work sheds light on the mechanism of action of IL-11 on CRP-inflammation. An IL-6 family cytokine, IL-11 likely possesses both anti-inflammatory and pro-inflammatory properties; it down-regulates macrophages and T cells at the site of inflammation, can skew immunity from a Th1 to Th2 phenotype, and regulates inflammatory processes in autoimmune disorders, inflammatory bowel disease, and psoriasis [51–56]. At the same time, IL-11 plays a role in antigen sensitization and Th2-inflammation [51], and is over-expressed in tuberculosis, arthritis, and cancer, potentially contributing to an inflammatory state in these disorders [51, 57, 58]. Our model deciphers the pro-inflammatory action mechanism of IL-11, by distinguishing between two pro-inflammatory effects that linearly change CRP levels, and occur on different time scales: one is a direct effect acting to rapidly and strongly elevate CRP,

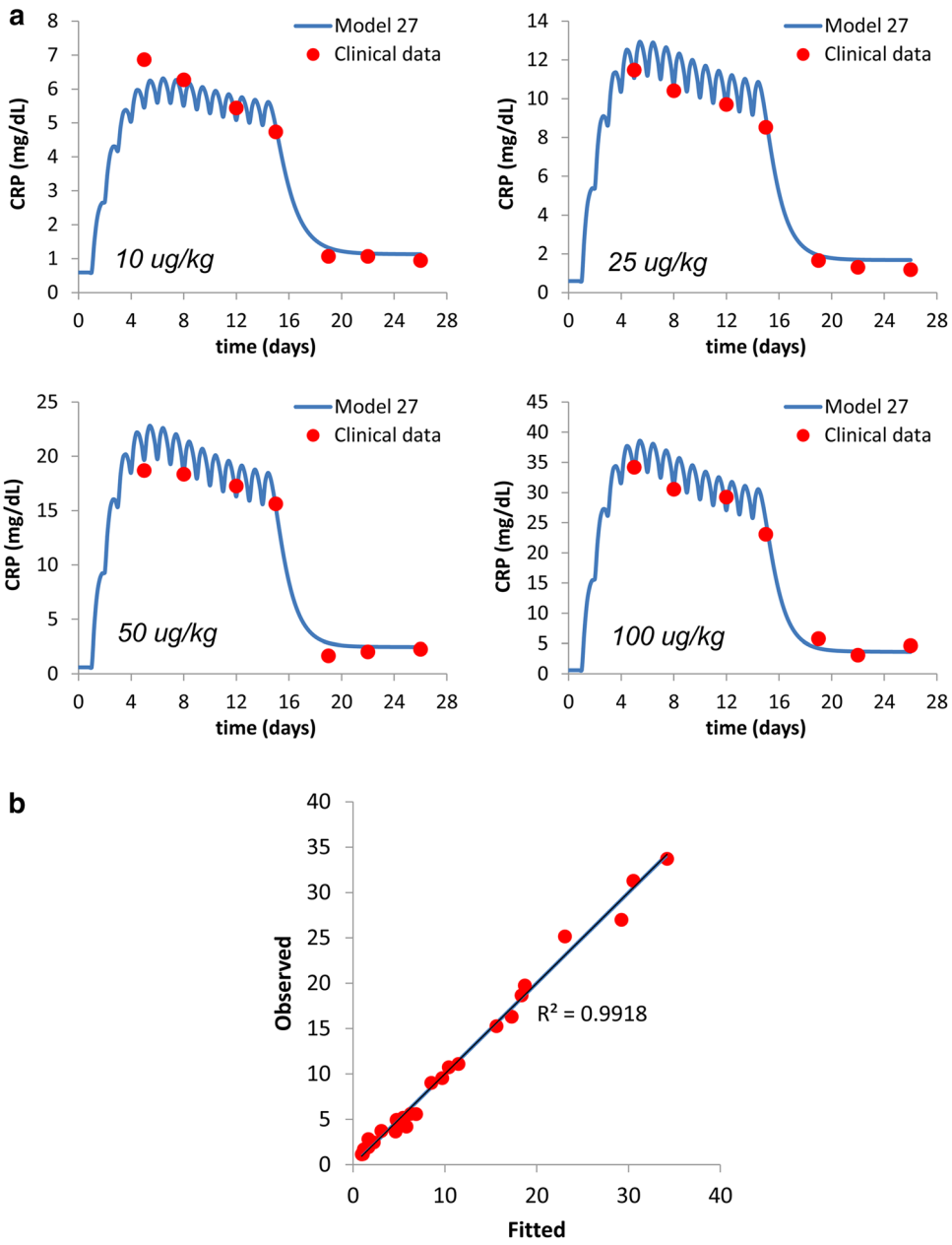

Fig. 4 Data fitting of the selected model to clinical CRP profiles. **a** Retrieval of observed inflammation (CRP) dynamics (mg/dl) by model 27. CRP was measured routinely following daily subcutaneous administration of IL-11 (10, 25, 50 and 75 μg/kg) for 2 weeks, as described in [17]. **b** Linear regression *curve* (*blue line*) and R^2 value of the fit is shown (Color figure online)

the other is a slower long-lasting effect responsible for low-grade elevation of CRP. The latter effect was imperative within the IL-11 mechanism, and was found to persist for at least a month, possibly more. Indeed, such continuous inflammation is a feasible outcome of any immune-modulating treatment (e.g. cytokine-based drugs, immunotherapies). For example, similar extended responses of delayed hypersensitivity are also detected several weeks post treatment with a different cytokine, IL-2 [59]. This mechanism of action, identified here for IL-11, may be valid for other immune modulating cytokines

The long term inflammation effect of IL-11, although not inflicting acute damage, is arguably most significant in a full-course regimen of the drug: Model simulations of multi-cycle therapy predict that while the CRP maximal peak is not further elevated under continued IL-11 scheduling, the CRP minima is expected to gradually increase between the cycles, reaching a detrimental level (above 3 mg/dl; Fig. 5). This low remains at a residual level slightly higher than baseline for at least 1 month, implying that chronic inflammation can result from the application of this cytokine. This result should be scrutinized experimentally and clinically over an extended period. If validated, it may bear clinical implications for therapy by this or other cytokine which have similar "memory" effects.

Table 2 Parameters of the best performing models

Parameter, units	Model 27		Model 28		Model 31	
	Value	SE (RSE)	Value	SE (RSE)	Value	SE (RSE)
γ_1	1	–	1	–	1	–
γ_2	1	–	1	–	1	–
a_1, days^{-2}	0.0671	0.02 (29)	0.0697	0.021 (30)	0.0669	0.02 (30)
a_2, days^{-1}						
ln(2)/a_2, day[a]	10.33	–	9.94	–	10.36	–
R_0	0.482	0.13 (26)	0.473	0.12 (26)	0.476	0.12 (26)
h_1	76.5	67 (88)	76.6	65 (84)	81.3	69 (85)
p_1	3.04	0.3 (10)	3.05	0.3 (10)	3.04	0.3 (10)
p_2	3.18	0.81 (25)	3.62	0.93 (26)	2.82	0.71 (25)
d	0.01	–	0.02	–	0.002	–
ln(2)/d[b]	69.31	–	34.66	–	346.6	–
C_0, mg/dl	0.594	–	0.594	–	0.594	–
a, mg/dl	0.935	0.14 (14)	0.933	0.14 (14)	0.934	0.14 (14)
a^1, mg/dl	1.62	0.24 (14)	1.62	0.24 (14)	1.62	0.24 (14)

a—residual constant error for averaged subjects

SE standard error, *RSE* relative standard error

a^1—residual constant error recalculated for individual subjects (see "Methods" section)

[a] Half time of the positive feedback

[b] Half time of M elimination

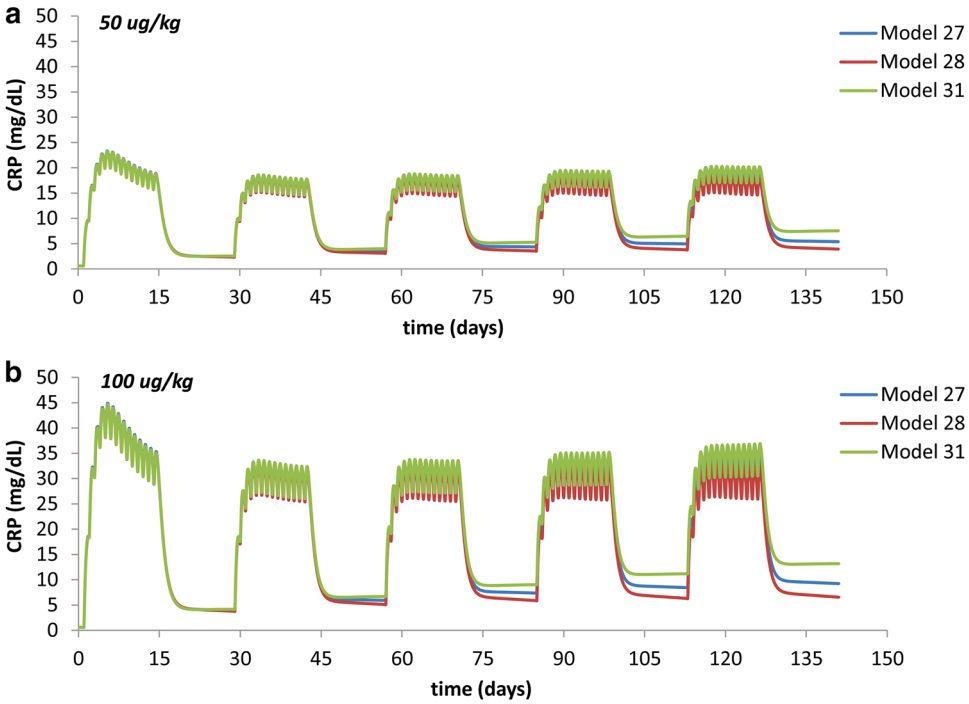

Fig. 5 Simulation of CRP dynamics under multi-cycle IL-11 treatment. Predictions of the CRP profile by model 27 and two equally-acceptable variants (28 and 31) under a regimen of 5 consecutive 28-days treatment cycles, where each cycle consists of a 2-week daily dosing of IL-11, 50 μg/kg (**a**) or 100 μg/kg (**b**), followed by a 2-week resting period

The model also provides interesting insights concerning CRP systemic behavior. A few models for studying CRP profiles have been presented hitherto. An early model used time-integrated CRP data to examine the use of this marker as a potential predictor for progression in rheumatoid arthritis [60, 61]. In another study, an elaborate biochemical model for the immune complement system showed that antibacterial responses are highly dependent on CRP activity [62]. Short-term oscillatory CRP dynamics in chemotherapy- or immunotherapy-treated melanoma patients were recently modeled as a means to better plan oncotherapy [23]. Here, we also modelled short-term CRP behavior in cancer patients, albeit under stimulation by IL-11. In absence of longitudinal CRP profiles in untreated cancer patients (over months-years), at present, no modeling effort can address the question of how cancer progression alters baseline systemic CRP dynamics. The present model itself illuminates a previously undescribed

process of self-induced clearance: We found that this clearance occurs in a nonlinear fashion, and is induced and reduced at the same rate. It is plausible that this self-regulation characterizes the inflammation process itself and not only its marker, CRP. This implies that humans can adapt their ability to resist inflammation to the intensity of the inflammatory process.

The unique modeling approach in the present work integrates mechanism-based biomathematical modelling of the bio-pharmaceutical process with statistical-oriented NLMEM evaluation of model parameters [8]. This allows to reach a sufficiently complex model for describing the system at hand, while at the same time accounting for individual data and random effects [63]. In contrast to statistical data-dependent models, in mechanistic modeling the data do not stand alone, but rather are intertwined with the biological understanding of cytokine-induced effects and feedback processes. This is especially important in cases where clinical measurements are imprecise, and in which long-range and feedback effects are difficult to assess by simple observation, as in the present IL-11 case. The inherent ability of mechanistic models to better extrapolate behavior for a wide range of treatment regimens beyond a given schedule is an additional advantage, particularly for rationing improved IL-11 treatment [8].

An important feature of our methodology is multiple-modeling, i.e. exhaustive, systematic, and objective analysis of several preliminary models in a "top-down" process. The designed models are semi-mechanistic, flexible and realistic structures that rely on a small number of assumptions about the underlying biological process. The collection of 35 models allowed us to examine diverse plausible assumptions and levels of complexity [8]. This differs from traditional hypothesis-driven biomathematical modeling, where usually preconceptions about the mechanism of action determine a single constructed model in a "bottom-up" process. Indeed, multi-model testing increases the probability of obtaining a good model [8]. A comparable multi-modeling method was applied in the past for modeling hematopoiesis and successfully retrieved population data under different chemotherapies, albeit with only 5 models undergoing assessment [64–67].

Moreover, our current study reports the systematic methodology, including model-building and qualification steps, criteria used for model selection, nature of the structural, IIV and error models, method of estimation and software, etc., details which are lacking, or are not reported, in most studies [68]. AIC was the primary model selection criterion, as it pinpoints the model that (a) retrieves the observed effect without being overly complex, and (b) which has the best chances of reproducing new independent data derived under similar conditions [39, 40]. Parsimony assumptions and linearizing processes were useful for efficient model screening, as they decreased the criteria values with no need to modify the mathematical formulation. Thus, such methodologies used during model development should be incorporated in similar reports dealing with progressive modeling.

Since our model is population-suited with minimal IIV assumptions (i.e. a minimal IIV was needed for describing the inflammation process herein), we can currently apply it to search a better IL-11 treatment policy for any patient. Specifically, the effect of long-term CRP accumulation, and how it may be restrained by altered IL-11 dosing regimens, is an important goal to study. Model-improved regimens have been suggested over the years for other targeted drugs, some validated pre-clinically and clinically [69–72]. Indeed, an alternative regimen with gradual IL-11 dose escalation is one promising strategy to replace the FDA-approved regimen of IL-11 (ongoing simulations; data not shown). Any such model-derived IL-11 regimens should of course be validated in prospective clinical studies prior to their application.

On a broader view, the findings in this study may bear implications for the design of diverse therapeutics that drive the immune system towards an inflamed phenotype, either directly (e.g. immunotherapeutic drugs) or indirectly (e.g. drugs that induce inflammation). We believe that the regimen planning of such agents should consider complex patterns of acute and chronic inflammation, perhaps by computational means.

Acknowledgments The authors thank Dr. Marina Kleiman, Prof. Gerard Wagemaker and Yuri Kogan for helpful discussions. This work was supported by the Chai Foundation.

Conflict of interest The authors declare that they have no conflict of interest.

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