A model analysis to measure the adherence of Etanercept and Fezakinumab therapy for the treatment of psoriasis*

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Articles

A model analysis to measure the adherence of Etanercept and Fezakinumab therapy for the treatment of psoriasis*

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Abstract: This article deals with a immunological model, which includes multiple classes of T cells, namely, the naive T cell, type I, type II and type 17 T helper cells (Th., Th., Th_{17}), regulatory T cell (T_{reg}) along with the activated natural killer cells (NK cells) and epidermal keratinocytes. In order to describe the etiology of psoriasis development, we have studied the basic mathematical properties of the model, existence and stability of the interior equilibrium. We have also derived the drug-induced mathematical model using impulse differential equation to determine the effects of combined biologics Etanercept (TNF-. inhibitor) and Fezakinumab (IL-22 monoclonal antibody) therapy considering perfect dosing during the inductive phase. We have determined the required dosing interval of both drugs to maintain the keratinocytes concentration below a threshold level. This study shows that Etanercept alone could theoretically maintain the keratinocytes level, whereas frequent dosing of Fezakinumab alone may not be enough to control the hyper-proliferation of keratinocytes. Furthermore, combination of the drugs with perfect dosing has the noticeable effect on keratinocytes dynamics, which may be suitable therapeutic approaches for treatment of psoriasis.
Keywords: keratinocytes, T helper cells, activated natural killer cells, immunological model, impulse differential equation.

1 Introduction

Psoriasis is a common, chronic inflammatory skin disease with a complex etiology involving immune disorder and environmental triggers. According to World Health Organization (WHO), it affects about 2% to 3% of the world population, although it is more prevalent in American, Canadian, and European populations [35]. This disease is characterized

by scaly red lesions on skin surface due to a huge proliferation of epidermal keratinocytes. Although, it is believed that psoriasis is a treatable but not curable disease, enlargement of treatment procedure is still in progress.

Biologic and biosimilar medications for psoriasis is the best current therapy proposed by many clinical and experimental researchers [20, 21]. These drugs fight with the causes rather than just eases the symptoms, and they target a specific part of body immune system. Specifically, biologics are used to suppress the action of a specific type of immune cells or they block some particular cytokines signaling. Tumor necrosis factor alpha ((TNF-α),), Interleukin 17 (IL-17) or Interleukin 12 (IL-12), Interleukin 23 (IL-12), etc. Over the past decades, several biological therapies have been approved based upon numerous parameters: FDA- and EU-approved indications, therapeutic efficacy and impact on quality of life, cost-effectiveness, and safety profile [4]. Though some biologics (Infliximab, Etanercept, Adalimumab, Efalizumab, etc.) have been already approved as therapeutic agent of psoriasis, yet researchers are still testing the efficacy of new biologics (Fezakinumab, Alefacept, etc.) [4,11]. Etanercept, (TNF-α), inhibitor, is accepted for the treatment of psoriasis at a dose of 25 mg or 50 mg twice weekly for 3 months followed by a maintenance dosage of 50 mg weekly thereafter [30,31]. This biologic binds with TNF-α (a Th$_1$ mediated cytokine that can bind to TNF receptor 1 or TNF receptor 2 and is involved in keratinocytes hyper-proliferation) to inhibit the inflammatory responses in skin which is characteristic of psoriasis [14, 17]. On the other hand, dendritic cells and keratinocytes mediated cytokine Interleukin IL-23 stimulates Th$_{17}$ cells within dermis to create IL-17A and IL-22,, which drives keratinocytes hyper-proliferation in psoriasis [6]. Many clinical trials suggested that Fezakinumab, a well-tolerated IL-22 monoclonal antibody, which is a promising therapeutic agent to treat epidermal hyperplasia and abnormal keratinocytes differentiation [9,19].

Recent evidence indicates that the activated NK cells release a large amount of IFN-γ, which lead the activation and hyper-proliferation of keratinocytes by the process of biochemical requirements [15, 33]. Activated NK cells mediated IFN-γ, has been shown to be a highly effective promoter of Th$_{17}$ cell trafficking to the skin in psoriasis [32]. Th. participate in promoting NK cell activation with enhanced cytotoxicity through Interleukin 21 (IL-21) signaling cascade [28]. T$_{reg}$, a new subpopulation of suppressor T cells, are typically known as inhibitors of autoimmune responses. For the psoriatic case, T$_{reg}$, can differentiate into inflammation-associated Th$_{17}$ cells (paradigm shift) [2]. Due to the pro-inflammatory cytokine milieu in the psoriasis lesion, especially high levels of Interleukin 6 IL-6 secreted from endothelial cells and Th$_{17}$ cells, which inhibit T$_{reg}$, activity [3]. The effects of two biologics (Etanercept and Fezakinumab) have been aggregated in this model by taking the mathematical approaches from [29] including some clinical data from [19,30,31].

Earlier, many researchers have discussed the dynamics of psoriasis to explore the etiology and possible treatment policies of psoriasis using mathematical models [12,16, 27]. Grigorieva and coworkers have studied

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the possible types of the control strategies associated with the first, second, and third orders singular arcs to enrich the control approach for the treatment of psoriasis [7,10]. Recently, Roy et al. have studied the impacts of T helper cells (Th$_1$, Th$_2$, and Th$_{17}$) along with the pro-inflammatory and anti-inflammatory cytokines on psoriasis progression and also discussed about the dominating roles of few biologics(IL-10, TNF-α inhibitor, IL-22 inhibitor) in the treatment of psoriasis [23–26].

In this research, a mathematical model has been formulated with an aim to study the etiology of psoriasis development including the dynamics of regulatory T cell (T$_{reg}$,) and activated natural killer cells (NK cells). Natural killer cells (type of lymphocyte and a component of innate immune system) become activated in presence of macrophage secreted cytokines, and that activated NK cells can produce various inflammatory cytokines (IFN-γ, TNF-α, etc.) [18, 34]. Here we have focused on the crucial role of regulatory T cell and activated NK cell along with the other T helper cells (naïve T cells, (Th$_1$, Th$_2$, and Th$_{17}$)) for capturing the excessive rapid proliferation of keratinocytes. We have observed the effect of Etanercept ((TNF-α), inhibitor) and Fezakinumab (IL-22 monoclonal antibody) therapy by considering impulse differential equation. We have determined the change in drug concentration, which occurs when a new dose is administered by using the impulsive model. We have found that the minimum dosing interval is required to maintain the keratinocyte density under a certain threshold. Furthermore, we have determined the efficacy of the combined drug doses as well as the individual drug doses through numerical analysis. It is also revealed that the Etanercept alone could theoretically maintain the keratinocytes level, but Fezakinumab alone may not be able to control the hyperproliferation of keratinocytes.

This manuscript is organized as follows. In the afterward Section 2, we have formulated the full mathematical model based on the above discussion. In Section 3, we have theoretically analyzed some basic properties of the system when no drugs is applied. In Section 4, we have investigated the impulse therapeutic approach with four extreme cases. The numerical outcomes of our formulated model (without and with therapy) have been demonstrated in Section 5. Finally, in Section 6, we have discussed the main results including the limitations, future scope, and novelty for our formulated mathematical system.

2 The model

In this section, we have formulated a mathematical system to describe the psoriasis dynamics by considering naive T cell, four different types of T helper cells Th$_1$, Th$_2$, Th$_{17}$, and T$_{reg}$,), activated natural killer cells (NK cells), and keratinocytes (skin cells). Here the density of naive T cell, Th$_1$, Th$_2$, Th$_{17}$, T$_{reg}$, activated natural killer cells (NK cells), and keratinocytes are represented by $T(t), T_1(t), T_2(t), T_{17}(t), T_{reg}(t), N_A(t)$, and $K(t)$, respectively, at any time .. The concentration of our considered two drugs (Etanercept and Fezakinumab) are represented by $E(t)$ and $F(t)$ at time $t \neq t_k$, where $k = 1, 2, \ldots, n.$

In order to develop the growth equation of naive T cell, we assume that a is the constant accumulation of naive T cells from bone marrow. Here we have considered that $\eta_i\ (i=1,2,3,4)$ are the production rate of Th$_1$, Th$_2$, Th$_{17}$, T$_{reg}$, respectively, from naive T cell. $\delta_i\ (i=1,2,3)$ represent the negative regulatory effect of Th$_2$ cell on naive T cell, Th$_1$, Th$_{17}$ cell, respectively, and γ_1 and γ_2 denote the negative regulatory effect of Th$_1$ cell on Th$_2$ and Th$_{17}$ cell, respectively. The inhibitory effect of Th$_{17}$ cell on Th$_1$ and T$_{reg}$, are denoted by β_1 and β_2, these inhibitory effects are associated with IL-17 and IL-6 cytokines signaling, respectively. We have assumed that ξ_1 and ξ_2 are the proliferation rate of Th$_1$ and Th$_2$, respectively, due to self released cytokines. Due to paradigm shift, T$_{reg}$, differentiate into Th$_{17}$, this rate is denoted by λ_1 and, at a rate λ_2 activated NK cells promote Th$_{17}$ through IFN-γ signaling cascade.

Let b be the constant accumulation of activated natural killer cells (NK cells) from bone marrow. Also, let ξ_3 and λ_3 are the proliferation rates of activated NK cells by the effect of self released and Th$_1$ mediated cytokines, respectively.

We assume that c is the constant growth of keratinocytes due to the constant migration of cells from dermal layer to epidermal layer. The effect of the vast IFN-γ released by activated NK cells, which help to proliferate the keratinocytes at a rate α_3. Furthermore, the positive regulatory effect of Th$_1$ and Th$_{17}$ cells on the proliferation of keratinocytes is given by the rate α_1 and α_2, respectively, and at the same time, Th$_2$ cells inhibit the proliferation of keratinocytes at the rate of δ_4. Natural death rates of naive T cell, Th$_1$, Th$_2$, Th$_{17}$, T$_{reg}$, activated natural killer cells, and keratinocytes are denoted by $\mu_i\ (i=1,2,\dots,7)$, respectively.

Based on the above assumptions and discussion, our formulated mathematical model to describe psoriasis dynamics is as follows:

$$
\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= a - \delta_1 T T_2 - \mu_1 T, \\
\frac{\mathrm{d}T_1}{\mathrm{d}t} &= \eta_1 T + \xi_1 T_1 - \delta_2 T_1 T_2 - \beta_1 T_{17} T_1 - \mu_2 T_1, \\
\frac{\mathrm{d}T_2}{\mathrm{d}t} &= \eta_2 T + \xi_2 T_2 - \gamma_1 T_1 T_2 - \mu_3 T_2, \\
\frac{\mathrm{d}T_{17}}{\mathrm{d}t} &= \eta_3 T + \lambda_1 T_{reg} + \lambda_2 N_A - \gamma_2 T_1 T_{17} - \delta_3 T_2 T_{17} - \mu_4 T_{17}, \\
\frac{\mathrm{d}T_{reg}}{\mathrm{d}t} &= \eta_4 T - \beta_2 T_{17} T_{reg} - \mu_5 T_{reg}, \\
\frac{dN_A}{\mathrm{d}t} &= b + \xi_3 N_A + \lambda_3 T_1 - \mu_6 N_A, \\
\frac{\mathrm{d}K}{\mathrm{d}t} &= c + \alpha_1 \left(\frac{E_{50}}{E_{50}+E}\right) T_1 + \alpha_2 \left(\frac{F_{50}}{F_{50}+F}\right) T_{17} \\
&\quad + \alpha_3 N_A - \delta_4 T_2 K - \mu_7 K.
\end{aligned}
\tag{1}
$$

In the seventh equation of system (1), the Hill functions $E_{50}/(E_{50}+E)$ and $F_{50}/(F_{50}+F)$ represent the degree to which Etanercept and Fezakinumab inhibit the positive regulatory effects of Th$_1$ and Th$_{17}$, respectively, on keratinocytes. Value of α_1 and α_2 decrease due to

the inhibitory effects of these two biologics. E_{50} and F_{50} represent the concentration of Etanercept and Fezakinumab, which required to inhibit hyper-proliferation of keratinocytes by 50%.

The dynamics of two drugs are described by the following:

$$\frac{dE}{dt} = -r_1 E \quad \text{for } t \neq t_k, \qquad \frac{dF}{dt} = -r_2 F \quad \text{for } t \neq \theta_j.$$
$$E(t_k^+) = E(t_k^-) + E_c \quad \text{for } t = t_k, \text{ where } k = 1, 2, \ldots, n.$$
$$F(\theta_k^+) = F(\theta_k^-) + F_c \quad \text{for } t = \theta_j, \text{ where } k = 1, 2, \ldots, n. \tag{2}$$

In system (2), r_1 and r_2 denote the rate at which the drugs are cleared. Here $E(t_k^+)$ and $F(\theta_k^+)$ are used to denote the concentration of Etanercept and Fezakinumab, respectively, at just after the Kth number of doses are taken. The concentration of these biologics at just before the intake of Kth number doses are represented by $E(t_k^+)$ and $F(\theta_k^+)$ Here E_c and F_c are the dosages of Etanercept and Fezakinumab, respectively, those drugs are taken at each impulse time $t = t_k$, where $k = 1, 2, \ldots, n$, and $t = \theta_k$ where $k = 1, 2, \ldots, n$. In general, $t_k \neq \theta_k$, so that the two drugs are taken at different times.

3 The system without drugs

When drugs are absent, i.e., $E = 0$ and $F = 0$, the system becomes:

$$\frac{dT}{dt} = a - \delta_1 T T_2 - \mu_1 T,$$
$$\frac{dT_1}{dt} = \eta_1 T + \xi_1 T_1 - \delta_2 T_1 T_2 - \beta_1 T_{17} T_1 - \mu_2 T_1,$$
$$\frac{dT_2}{dt} = \eta_2 T + \xi_2 T_2 - \gamma_1 T_1 T_2 - \mu_3 T_2,$$
$$\frac{dT_{17}}{dt} = \eta_3 T + \lambda_1 T_{\text{reg}} + \lambda_2 N_A - \gamma_2 T_1 T_{17} - \delta_3 T_2 T_{17} - \mu_4 T_{17}, \tag{3}$$
$$\frac{dT_{\text{reg}}}{dt} = \eta_4 T - \beta_2 T_{17} T_{\text{reg}} - \mu_5 T_{\text{reg}},$$
$$\frac{dN_A}{dt} = b + \xi_3 N_A + \lambda_3 T_1 - \mu_6 N_A,$$
$$\frac{dK}{dt} = c + \alpha_1 T_1 + \alpha_2 T_{17} + \alpha_3 N_A - \delta_4 T_2 K - \mu_7 K$$

subject to the following initial conditions:

$$T(0) \geqslant 0, \qquad T_1(0) \geqslant 0, \qquad T_2(0) \geqslant 0, \qquad T_{17}(0) \geqslant 0,$$
$$T_{\text{reg}}(0) > 0, \qquad N_A(0) > 0, \qquad K(0) \geqslant 0.$$

In this section, we have studied the boundedness property of the solutions of system (3). We have also discussed the existence of the interior equilibria and stability criteria.

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3.1 Boundedness

It is very important to establish that all the model variables are bounded for all time t. This will ensure that the model is well-posed and plausible to represent the cell populations. The following theorem describes the boundedness of the solutions of system (3).

Theorem 1. All the solutions of system (3) enter into the region $\Omega \subset \mathbb{R}_+^7$ and are ultimately bounded, where Ω is defined as

$$
\begin{aligned}
\Omega = \big\{ (T, T_1, T_2, T_{17}, T_{\mathrm{reg}}, N_A, K)^\top \in \mathbb{R}_+^7 : \; & 0 \leqslant T \leqslant M_1, \\
& 0 \leqslant T_1 \leqslant M_2, \; 0 \leqslant T_2 \leqslant M_3, \; 0 \leqslant T_{17} \leqslant M_4, \\
& 0 \leqslant T_{\mathrm{reg}} \leqslant M_5, \; 0 \leqslant N_A \leqslant M_6, \; 0 \leqslant K \leqslant M_7 \big\},
\end{aligned}
$$

if the following conditions hold:

$$
\begin{aligned}
& T(0) \geqslant 0, \qquad T_1(0) \geqslant 0, \qquad T_2(0) \geqslant 0, \qquad T_{17}(0) \geqslant 0, \\
& \qquad T_{\mathrm{reg}}(0) > 0, \qquad N_A(0) > 0, \qquad K(0) \geqslant 0.
\end{aligned}
$$

and

$$
\mu_6 > \xi_3, \qquad \mu_2 > \xi_1, \qquad \mu_3 > \xi_2.
$$

Here the symbol "$\top$" denotes the transpose, and M_i, $i = 1, 2, \ldots, 7$, are defined by the following formulas:

$$
\begin{aligned}
& M_1 = \frac{a}{\mu_1}, \qquad M_2 = \frac{\eta_1 M_1}{\mu_2 - \xi_1}, \qquad M_3 = \frac{\eta_2 M_1}{\mu_3 - \xi_2}, \qquad M_4 = \frac{\eta_3 M_1 + \lambda_1 M_5 + \lambda_2 M_6}{\mu_4}, \\
& \qquad M_5 = \frac{\eta_4 M_1}{\mu_5}, \qquad M_6 = \frac{b + \lambda_3 M_2}{\mu_6 - \xi_3}, \qquad M_7 = \frac{c + \alpha_1 M_2 + \alpha_2 M_4 + \alpha_3 M_6}{\mu_7}.
\end{aligned}
$$

Proof. Let us consider the first equation of system (3) and neglecting the term $\delta_1 T T_2$, we have the relationship:

$$
\frac{\mathrm{d}T}{\mathrm{d}t} < a - \mu_1 T. \tag{4}
$$

By applying the well-known comparison principle described by [1] to (4) and considering $M_1 = a/\mu_1$, we obtain the inequality

$$
0 < T_1(t) < M_1\big(1 - \mathrm{e}^{-\mu_1 t}\big) + T(0)\mathrm{e}^{-\mu_1 t}, \quad t > 0,
$$

from which it follows that $T(t) \leqslant M_1$ if $T(0) \leqslant M_1$. By using similar arguments (one can see [25] for detail analysis) we can easily show that all solutions $(T, T_1, T_2, T_{17}, T_{\mathrm{reg}}, , N_A, K)^\top$ of system (3) that start in Ω remain in this set for all

$t > 0$. It means that . is invariant set of this system. Moreover, the region . is bounded, and therefore, all mentioned solutions ultimately bounded.

3.2 Equilibrium analysis

Here we have considered interior equilibrium (I_E) as a steady state solution where the disease persists.

For the existence of interior equilibrium $I_E = (T^*, T_1^*, T_2^*, T_{17}^*, T_{\text{reg}}^*, N_A^*, K^*)^\top$, its coordinates should satisfy the conditions: $T^* > 0, T_1^* > 0, T_2^* > 0, T_{17}^* > 0, T_{\text{reg}}^* > 0, N_A^* > 0, K^* > 0.$ In order to obtain the existence condition of the interior equilibrium, we set the first, second, third, fifth, sixth, and seventh equations of system (3) to zero. Solving state variables in terms of T_2^*, we obtain the following:

$$
\begin{aligned}
T^* &= \frac{a}{\delta_1 T_2^* + \mu_1}, \qquad T_1^* = \frac{\eta_2 T^* + (\xi_2 - \mu_3)T_2^*}{\gamma_1 T_2^*}, \\
T_{17}^* &= \frac{\eta_1 T^* + (\xi_1 - \delta_2 T_2^* - \mu_2)T_1^*}{\beta_1 T_1^*}, \\
T_{\text{reg}}^* &= \frac{\eta_4 T^*}{\beta_2 T_{17}^* + \mu_5}, \qquad N_A^* = \frac{b + \lambda_3 T_1^*}{\mu_6 - \xi_3}, \\
K^* &= \frac{c + \alpha_1 T_1^* + \alpha_2 T_{17}^* + \alpha_3 N_A^*}{\delta_4 T_2^* + \mu_7}.
\end{aligned}
\tag{5}
$$

Now using the values expressed in system (5), we have obtained the tenth degree polynomial of T_2^*, from the fourth equation of system (3). Now, we compare with the standard form

$$
\begin{aligned}
f(T_2^*) = {}& T_2^{*10} + B_9 T_2^{*9} + B_8 T_2^{*8} + B_7 T_2^{*7} + B_6 T_2^{*6} + B_5 T_2^{*5} \\
& + B_4 T_2^{*4} + B_3 T_2^{*3} + B_2 T_2^{*2} + B_1 T_2^* + B_0.
\end{aligned}
\tag{6}
$$

Since it is hard to evaluate all coefficients, viz. $B_i \ (i = 1, 2, \dots, 9)$ so we can construct the following lemma to conclude the existence criteria by using the fact that if $B_0 < 0$, then it has at least one positive root in $[0, \infty)$.

Lemma 1. *If* $\lambda_2 \lambda_3 + \gamma_2 \mu_3 > \gamma_2 \xi_1 (\mu_6 - \xi_3)$ *holds, then there exists an interior equilibrium point I. of system* (1).

Analytically, it is also very difficult to determine the steady state values of system populations. We have determined numerically by performing the numerical stability analysis. For the stability analysis, we need the Jacobian at any steady point at I_E

$$
J(I_E) = \begin{bmatrix}
-\frac{a}{T^*} & 0 & -\delta_1 T^* & 0 & 0 & 0 & 0 \\
\eta_1 & -\frac{\eta_1 T^*}{T_1^*} & -\delta_2 T_1^* & -\beta_1 T_{17}^* & 0 & 0 & 0 \\
\eta_2 & -\gamma_1 T_2^* & -\frac{\eta_2 T^*}{T_2^*} & 0 & 0 & 0 & 0 \\
\eta_3 & -\gamma_2 T_{17}^* & -\delta_3 T_{17}^* & -(\gamma_2 T_1^* + \delta_3 T_2^* + \mu_4) & \lambda_1 & \lambda_2 & 0 \\
\eta_4 & 0 & 0 & -\beta_2 T_{\text{reg}}^* & -\frac{\eta_4 T^*}{T_{\text{reg}}^*} & 0 & 0 \\
0 & \lambda_3 & 0 & 0 & 0 & \xi_3 - \mu_6 & 0 \\
0 & \alpha_1 & -\delta_4 K^* & \alpha_2 & 0 & \alpha_3 & -(\delta_4 T_2^* + \mu_7)
\end{bmatrix}.
$$

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The matrix $J(I_E)$ has characteristic equation

$$(\chi + \delta_4 T_2^* + \mu_7) \det \mathcal{M}(I_E) = 0,$$

where

$$\mathcal{M}(I_E) = \begin{bmatrix} -\frac{a}{T^*} - \chi & 0 & -\delta_1 T^* & 0 & 0 & 0 \\ \eta_1 & -\frac{\eta_1 T^*}{T_1^*} - \chi & -\delta_2 T_1^* & -\beta_1 T_{17}^* & 0 & 0 \\ \eta_2 & -\gamma_1 T_2^* & -\frac{\eta_2 T^*}{T_2^*} - \chi & 0 & 0 & 0 \\ \eta_3 & -\gamma_2 T_{17}^* & -\delta_3 T_{17}^* & -(\gamma_2 T_1^* + \delta_3 T_2^* + \mu_4) - \chi & \lambda_1 & \lambda_2 \\ \eta_4 & 0 & 0 & -\beta_2 T_{\mathrm{reg}}^* & -\frac{\eta_4 T^*}{T_{\mathrm{reg}}^*} - \chi & 0 \\ 0 & \lambda_3 & 0 & 0 & 0 & (\xi_3 - \mu_6) - \chi \end{bmatrix}.$$

Let elements of the above matrix $\mathcal{M}(I_E)$ are in the form of a_{ij}, where $\{i, j \in (1, 2, \dots, 6)\}$. Now, $\det \mathcal{M}(I_E)$ gives

$$\chi^6 + A_1 \chi^5 + A_2 \chi^4 + A_3 \chi^3 + A_4 \chi^2 + A_5 \chi + A_6 = 0,$$

where $A_i, \, i = 1, 2, \dots, 6,$ are the coefficient of the above polynomial. The coefficients are defined as

$$A_1 = -\sum a_{ij},$$
$$A_2 = \sum a_{ii} a_{jj} - \sum a_{ij} a_{ji}$$
$$A_3 = \sum a_{ij} a_{ji} a_{kk} - \sum a_{ii} a_{jj} a_{kk} - \sum a_{ij} a_{jk} a_{ki}$$
$$A_4 = \sum a_{ii} a_{jj} a_{kk} a_{ll} + \sum a_{ij} a_{ji} a_{ki} a_{ll} + \sum a_{ij} a_{ji} a_{kl} a_{lk} - \sum a_{ij} a_{ji} a_{kk} a_{ll}$$
$$\quad - \sum a_{ij} a_{ji} a_{kl} a_{li}$$
$$A_5 = \sum a_{ij} a_{ji} a_{kk} a_{ll} a_{mm} - \sum a_{ii} a_{jj} a_{kk} a_{ll} a_{mm} - \sum a_{ij} a_{jk} a_{kl} a_{li} a_{mm}$$
$$\quad - \sum a_{ij} a_{jk} a_{ki} a_{ll} a_{mm} - \sum a_{ij} a_{ji} a_{kl} a_{lk} a_{mm} + \sum a_{ij} a_{jk} a_{kl} a_{lm} a_{mi}$$
$$A_6 = \sum a_{ii} a_{jj} a_{kk} a_{ll} a_{mm} a_{nn} + \sum a_{ij} a_{jk} a_{kl} a_{lm} a_{mi} a_{nn} + \sum a_{ij} a_{ji} a_{kl} a_{lk} a_{mm} a_{nn}$$
$$\quad + \sum a_{ij} a_{jk} a_{ki} a_{lm} a_{mn} a_{nl} - \sum a_{ij} a_{ji} a_{kk} a_{ll} a_{mm} a_{nn} - \sum a_{ij} a_{ji} a_{kl} a_{lm} a_{mk} a_{nn}.$$

Here $A_i, \, i = 1, 2, \dots, 6,$ followed a rule that $i \neq j \neq k \neq l \neq m \neq n$. In a_{ij}, if $i = 1$, then j can go to 6 or 5. Following same rule for k, l, m, n. Similarly, 2 can go 5 or 6, 3 can go 5, 4 can go 5 or 3, 5 can go 2 or 3 or 4 or 6, and 6 can go 1 or 2 or 5. In $a_{ij} a_{ji}$, let $i = 1$, then j can go 5 or 6, but $a_{15} a_{51}$ does not exist because 5 cannot go to 1. For example, applying the above rule, we get the expression of A_2 as follows:

$$A_2 = \sum_{i=1}^{5} a_{ii} \sum_{j=i+1}^{6} a_{jj} - \{ a_{16} a_{61} + a_{26} a_{62} + a_{25} a_{52} + a_{35} a_{53} + a_{45} a_{54} + a_{56} a_{65} \}.$$

Now, we can conclude the stability criteria by the following remark.

Remark 1. All the roots of the characteristic equation are negative or have negative real part if the determinants of all the Hurwitz matrices are positive, i.e., $\det(H_j) > 0, \, j = 1, 2, \dots, 6$. Thus, according to the Routh–Hurwitz

criterion [8, 22], the system is asymptotically stable if $det(H_j) > 0, j = 1, 2, \ldots, 6,$ where the Hurwitz matrices are given by

$$H_1 = (A_1), \qquad H_2 = \begin{pmatrix} A_1 & 1 \\ 0 & A_2 \end{pmatrix},$$

$$H_3 = \begin{pmatrix} A_1 & 1 & 0 \\ A_3 & A_2 & A_1 \\ 0 & 0 & A_3 \end{pmatrix}, \qquad H_4 = \begin{pmatrix} A_1 & 1 & 0 & 0 \\ C & A_2 & A_1 & 1 \\ 0 & A_4 & A_3 & A_2 \\ 0 & 0 & 0 & A_4 \end{pmatrix}$$

$$H_5 = \begin{pmatrix} A_1 & 1 & 0 & 0 & 0 \\ A_3 & A_2 & A_1 & 1 & 0 \\ A_5 & A_4 & A_3 & A_2 & A_1 \\ 0 & 0 & A_5 & A_4 & A_3 \\ 0 & 0 & 0 & 0 & A_5 \end{pmatrix} \quad \text{and} \quad H_6 = \begin{pmatrix} A_1 & 1 & 0 & 0 & 0 & 0 \\ A_3 & A_2 & A_1 & 1 & 0 & 0 \\ A_6 & A_5 & A_4 & A_3 & A_2 & A_1 \\ 0 & A_6 & A_5 & A_4 & A_3 & A_2 \\ 0 & 0 & 0 & A_6 & A_5 & A_4 \\ 0 & 0 & 0 & 0 & 0 & A_6 \end{pmatrix}.$$

4 The system with drugs

In this section, we have analyzed the drug-induced system using modified impulsive method to evaluate the dosing interval. The consideration of impulsive differential equations to measure the drug adherence will obviously perturb the interior steady state. Due to these impulse effect, the solutions of our formulated model exhibit periodic orbits with discontinuities. It is clear from models (1), (2) that only the drugs will exhibit discontinuities directly, and the other parameters may have discontinuities in their derivatives, but will have continuous solutions.

Here we have considered that the drugs (Etanercept and Fezakinumab) are given at fixed intervals. Let $\tau = t_{k+1} - t_k$ be the period of Etanercept (TNF-α inhibitor), and let $\sigma = \theta_{j+1} - \theta_j$ be the period of Fezakinumab (IL-22 monoclonal antibody) (for $k, j \geqslant 1$). For t satisfying $t_{k+1} < t < t_k$ and $\theta_{j+1} < t < \theta_j$, we have

$$E(t) = E(t_k^+)e^{-r_1(t-t_k)}, \qquad F(t) = F(\theta_j^+)e^{-r_2(t-\theta_j)}. \tag{7}$$

The recursion relation at the moments of impulse is given by

$$E(t_k^+) = E(t_k^-) + E_c, \qquad F(\theta_j^+) = F(\theta_j^-) + F_c. \tag{8}$$

From the first equation of system (7) along with the recursion relation (8), we have obtained

$$E(t_k^+) = E_c \frac{1 - e^{-kr_1\tau}}{1 - e^{-r_1\tau}} \rightarrow \frac{E_c}{1 - e^{-r_1\tau}}$$

as $k \to \infty$. Similarly, as $j \to \infty$, we have

$$F(\theta_j^+) \to \frac{F_c}{1 - e^{-r_2\sigma}}.$$

In order to obtain the ends of a positive impulsive periodic orbit of Etanercept, we have considered

$$E(t_{k+1}^+) = E(t_{k+1}^-) + E_c, = \frac{E_c}{1 - e^{-r_1\tau}} e^{-r_1\tau} + E_c, = \frac{E_c}{1 - e^{-r_1\tau}}.$$

Furthermore,

$$E(t_k^+) - \frac{E_c}{1 - e^{-r_1\tau}} = E_c \frac{1 - e^{-kr_1\tau}}{1 - e^{-r_1\tau}} - \frac{E_c}{1 - e^{-r_1\tau}}, = -E_c \frac{e^{-kr_1\tau}}{1 - e^{-r_1\tau}}.$$

Hence, the ends of a positive impulsive periodic orbit of Etanercept has been defined by the impulse points $E_c/(1 - e^{-r_1\tau})$ and $E_c e^{-r_1\tau}/(1 - e^{-r_1\tau})$ to which the endpoints of each cycle monotonically increase.

Similarly, the ends of a positive impulsive periodic orbit of Fezakinumab has been defined by the impulse points $F_c/(1 - e^{-r_2\sigma})$ and $F_c e^{-r_2\sigma}/(1 - e^{-r_2\sigma})$ to which the endpoints of each cycle monotonically increase.

4.1 Extreme cases analysis

Here we have analyzed four extreme cases to manifest the different outcomes that can occur depending on the dosing intervals. Before analysing the case, we cite the following lemma from [29].

Lemma 2. *Suppose x is a variable satisfying*

$$\frac{dx}{dt} < c - q(\phi)x(t),$$

where c is a constant, and $q(\phi)$ is independent of x and t. Then i if $x(0) < c/q(\phi)$, it follows that $x(t) < c/q(\phi)$ for all t.

We have considered that a small dosing interval corresponds to frequent drug administration. It is obvious that small dosing intervals should provide the most effective therapy, whereas large dosing intervals should have little effect on over proliferated keratinocytes. We have also considered $\bar{K}$, the normal keratinocytes density. The value of $\bar{K}$, has been taken 200 mm^{-3}. Our target is to keep the keratinocytes density below $\bar{K}$, by administrating drug with suitable dosing interval. Furthermore, only the keratinocytes population has been considered in describing the following four extreme cases depending on the dosing intervals. In order to avoid mathematical complexity, we have ignored the effect of drugs on the other immune cells.

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The initial conditions on the drug concentrations and the monotonicity of the impulsive trajectories imply that

$$E(t) < \frac{E_c}{1 - e^{-r_1\tau}} \quad \text{and} \quad F(t) < \frac{F_c}{1 - e^{-r_2\sigma}}$$

for all .. Since the impulsive drug orbits are asymptotically stable, it follows that for any $\varepsilon > 0$, there exists t_1 such that

$$E(t) < \frac{E_c}{1 - e^{-r_1\tau}} \quad \text{and} \quad F(t) < \frac{F_c}{1 - e^{-r_2\sigma}}$$

Case 1. Absence of both drugs (i.e., $E(t) = 0$ and $F(t) = 0$).

If no drugs have been applied, then we can consider the situation where Th_1 Th_{17} and activated NK cells dominate, while Th_2 is present at the low density level. By using Theorem 1 we can consider the keratinocytes density as follows:

$$\frac{dK}{dt} < c + \alpha_1 M_2 + \alpha_2 M_4 + \alpha_3 M_6 - \mu_7 K, \qquad K(t) < M_7,$$

where M_2, M_4, M_6, M_7 have been defined in Theorem 1. Here we have concluded by the following remark.

Remark 2. Drugs will be applied when the keratinocytes density $K(t)$ satisfies the condition $\tilde{K} < \bar{K}(t) < M_7$ for any time t. Note that keratinocytes density at interior equilibrium K^* also satisfies the condition $\tilde{K} < K^* < M_7$.

Case 2. The absence of Fezakinumab (i.e., $F(t) = 0$) *but frequent use of Etanercept.* Here, for a fixed value of ε, the dynamics of keratinocyte is described as follows:

$$\frac{dK}{dt} < c + \alpha_1 \left(\frac{E_{50}}{E_{50} + E_c e^{-r_1\tau}/(1 - e^{-r_1\tau}) - \varepsilon} \right) M_2$$
$$+ \alpha_2 M_4 + \alpha_3 M_6 - \mu_7 K,$$
$$K(t) < \frac{\Psi(\tau)}{\mu_7}.$$

Suppose that Etanercept is applied at dosing interval, i.e., τ_1 for which keratinocytes density will be less than or equal to $\tilde{K}$. Hence, the following inequality holds:

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$$\frac{\Psi(\tau_1)}{\mu_7} \leqslant \tilde{K},$$

$$\alpha_1 \left(\frac{E_{50}}{E_{50} + E_c e^{-r_1 \tau_1}/(1 - e^{-r_1 \tau_1}) - \varepsilon} \right) M_2 \leqslant \mu_7 \tilde{K} - (c + \alpha_2 M_4 + \alpha_3 M_6),$$

$$\frac{e^{-r_1 \tau_1}}{1 - e^{-r_1 \tau_1}} \geqslant \frac{\alpha_1 M_2 E_{50}}{E_c(\mu_7 \tilde{K} - c - \alpha_2 M_4 - \alpha_3 M_6)} - \frac{E_{50}}{E_c} + \frac{\varepsilon}{E_c},$$

$$\tau_1 \leqslant \frac{1}{r_1} \ln \left| \frac{\Lambda}{1 + \Lambda} \right|, \tag{9}$$

where

$$\Psi(\tau_1) = c + \alpha_1 \left(\frac{E_{50}}{E_{50} + E_c e^{-r_1 \tau_1}/(1 - e^{-r_1 \tau_1}) - \varepsilon} \right) M_2 + \alpha_2 M_4 + \alpha_3 M_6,$$

$$\Lambda = \frac{\alpha_1 M_2 E_{50}}{E_c(\mu_7 \tilde{K} - c - \alpha_2 M_4 - \alpha_3 M_6)} - \frac{E_{50}}{E_c} + \frac{\varepsilon}{E_c}.$$

From (9) we get the upper value of dosing interval of the frequent dose of Etanercept. By the following remark we can conclude this case.

Remark 3. In absence of Fezakinumab, if only Etanercept is applied at the dosing interval τ_1, described in equation (9) the keratinocytes density will be less than or equal to $\tilde{K}$. For a fixed value of ε, we can determine the value of τ_1, which have been demonstrated in numerical section.

Case 3. The absence of Etanercept (i.e., $E(t) = 0$) *but frequently use of Fezakinumab.* Here, for a fixed value of ε, the dynamics of keratinocyte is described as follows:

$$\frac{dK}{dt} < c + \alpha_1 M_2 + \alpha_2 \left(\frac{F_{50}}{F_{50} + F_c e^{-r_2 \sigma}/(1 - e^{-r_2 \sigma}) - \varepsilon} \right) M_4 + \alpha_3 M_6 - \mu_7 K,$$

$$K(t) < \frac{\Psi(\sigma)}{\mu_7}.$$

Again, suppose that Fezakinumab is applied at dosing interval, i.e., σ_1 for which keratinocytes density will be less than or equal to K^*. Hence, by using Lemma 2 the following inequality can be established:

$$\frac{\Psi(\sigma_1)}{\mu_7} \leqslant \tilde{K},$$

$$\alpha_2 \left(\frac{F_{50}}{F_{50} + F_c e^{-r_2 \sigma_1}/(1 - e^{-r_2 \sigma_1}) - \varepsilon} \right) M_4 \leqslant \mu_7 \tilde{K} - (c + \alpha_1 M_2 + \alpha_3 M_6),$$

$$\frac{e^{-r_2 \sigma_1}}{1 - e^{-r_2 \sigma_1}} \geqslant \frac{\alpha_2 M_4 F_{50}}{F_c(\mu_7 \tilde{K} - c - \alpha_1 M_2 - \alpha_3 M_6)} - \frac{F_{50}}{F_c} + \frac{\varepsilon}{F_c},$$

$$\sigma_1 \leqslant \frac{1}{r_2} \ln \left| \frac{\Omega}{1 + \Omega} \right|, \tag{10}$$

where

$$\Psi(\sigma_1) = c + \alpha_1 M_2 + \alpha_2 \left(\frac{F_{50}}{F_{50} + F_c e^{-r_2\sigma_1}/(1 - e^{-r_2\sigma_1}) - \varepsilon} \right) M_4 + \alpha_3 M_6,$$

$$\Omega = \frac{\alpha_2 M_4 F_{50}}{F_c(\mu_7 \tilde{K} - c - \alpha_1 M_2 - \alpha_3 M_6)} - \frac{F_{50}}{F_c} + \frac{\varepsilon}{F_c}.$$

From (10) we get the upper bound of dosing interval of the frequent dose of Fezakinumab. By the following remark we make a conclusion on Case 3.

Remark 4. In absence of Etanercept, if only Fezakinumab is applied at the dosing interval σ_1, described in equation (10) the keratinocytes density will be less than or equal to $\tilde{K}$. For a fixed value of ε, we can determine the value of σ_1, which have been demonstrated in numerical section.

Case 4. Frequent dosing of both drugs.

Here we have recalled inequalities (9) and (10) to describe the case when Etanercept and Fezakinumab are taken frequently. τ^* and σ^* are the fixed dosing intervals of Etanercept and Fezakinumab. Hence, for a fixed value of ε, the dynamics of keratinocyte is described as follows:

$$\frac{dK}{dt} < c + \alpha_1 \left(\frac{E_{50}}{E_{50} + E_c e^{-r_1\tau^*}/(1 - e^{-r_1\tau^*}) - \varepsilon} \right) M_2$$

$$+ \alpha_2 \left(\frac{F_{50}}{F_{50} + F_c e^{-r_2\sigma^*}/(1 - e^{-r_2\sigma^*}) - \varepsilon} \right) M_4$$

$$+ \alpha_3 M_6 - \mu_7 K,$$

$$K(t) < \frac{\Upsilon(\sigma^*, \tau^*)}{\mu_7}.$$

Hence, the following inequality holds:

$$\frac{\Upsilon(\sigma^*, \tau^*)}{\mu_7} \leqslant \tilde{K},$$

Where

$$\Upsilon(\sigma^*, \tau^*) = c + \alpha_1 \left(\frac{E_{50}}{E_{50} + E_c e^{-r_1\tau^*}/(1 - e^{-r_1\tau^*}) - \varepsilon} \right) M_2$$

$$+ \alpha_2 \left(\frac{F_{50}}{F_{50} + F_c e^{-r_2\sigma^*}/(1 - e^{-r_2\sigma^*}) - \varepsilon} \right) M_4$$

$$+ \alpha_3 M_6. \tag{11}$$

We write our conclusion on Case 4 in the following remark.

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Remark 5. If Etanercept and Fezakinumab are taken frequently at the dosing interval τ^* and σ^* satisfying inequalities (9) and (10), then for a fixed value of ε, we can determine the value of τ^* and σ^* by using inequality (11).

5 Numerical simulations and discussion

In this section, we have performed the numerical simulations of the mathematical systems (1), (2), and (3) to understand the analytic results. First, we have shown the solution of different cells and their effects on the psoriatic dynamics that is reflected in the model (without drug). Then the dynamical behavior of keratinocytes have been numerically evaluated under impulse therapeutic approach. The corresponding drugs (Etanercept and

Parameter	Value [Day^{-1}]	Parameter	Value [Day^{-1}]	Parameter	Value [Day^{-1}]
α_1	0.2	δ_4	0.028	μ_3	0.1
α_2	0.2	η_1	0.06	μ_4	0.2
α_3	0.005	η_2	0.003	μ_5	0.03
β_1	0.001	η_3	0.06	μ_6	0.3
β_2	0.004	η_4	0.06	μ_7	0.05
γ_1	0.0002	λ_1	0.03	ξ_1	0.02
γ_2	0.0002	λ_2	0.04	ξ_2	0.02
δ_1	0.002	λ_3	0.0014	ξ_3	0.045
δ_2	0.002	μ_1	0.12	r_1	0.25
δ_3	0.036	μ_2	0.05	r_2	0.25
$a = 25$ mm^{-3}Day^{-1}		$b = 10$ mm^{-3}Day^{-1}		$c = 30$ mm^{-3}Day^{-1}	

Table 1.

Values of the system parameter used in numerical simulations. For the choice of parameters values, we have found the ranges of few parameters from literatures [23–26]. Many of the model parameters are estimated from different literatures [5, 13, 16] that allowed model behaviour to be biologically feasible.
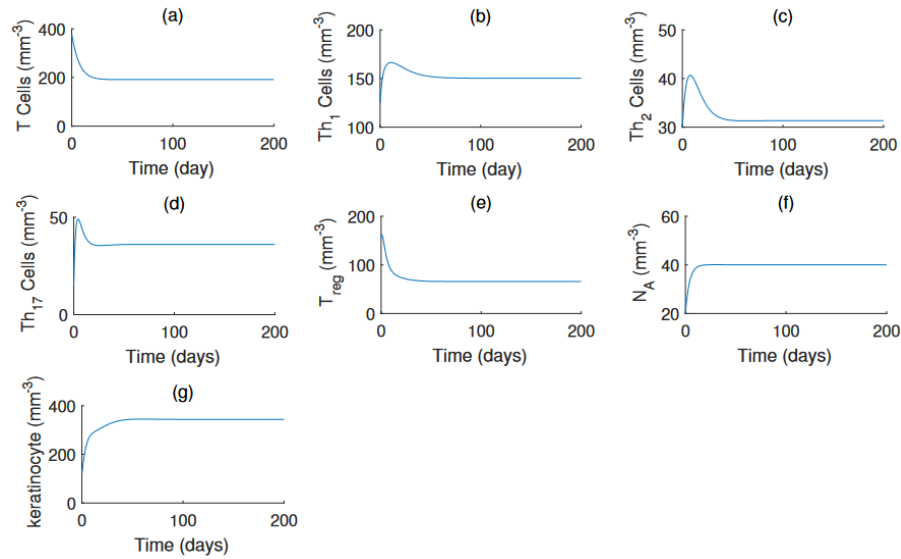
Figure 1.

Time series solutions of our formulated system (3), which demonstrate the qualitative nature of all cells (naive T cells, Th1 cells, Th2 cells, Th17 cells, regulatory T cells, activated NK cells, and keratinocytes) during the disease progression. Parameter's values are taken from Table 1.

Fezakinumab) dynamics also have been demonstrated. Parameter's value used for numerical simulations are listed in Table 1.

In Fig. 1, we have plotted the numerical solution of considered immune cells (naive T cell, Th₁ cell, Th₂ cell, Th₁₇ cell, regulatory T cell, activated NK cell) and keratinocytes to investigate the qualitative behavior of model populations for psoriatic state. This figure manifests that the psoriatic situation is dominated by T Th₁, Th₁₇., and activated NK cells as well as Th₂, and regulatory T cell are in suppressed condition. In presence of various pro-inflammatory cytokines (released by Th₁, Th₁₇, and activated NK cells) the

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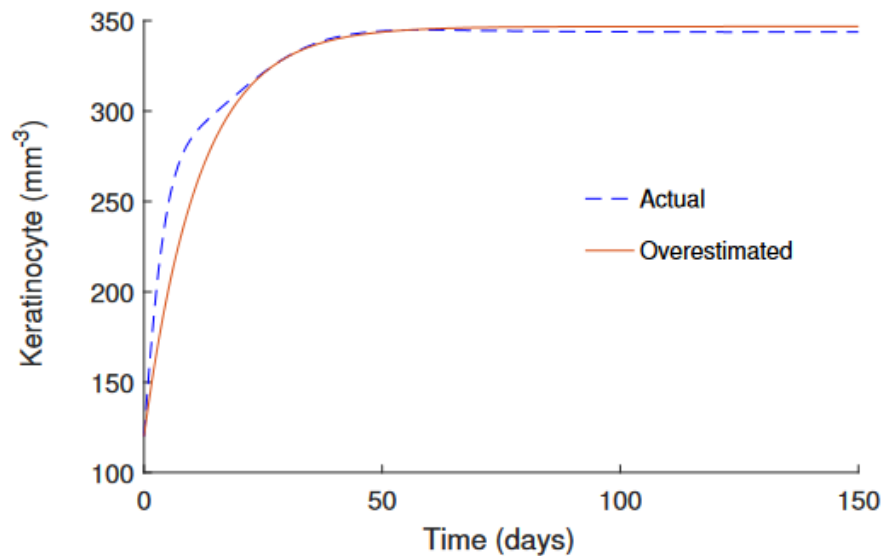
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Figure 2.
Comparison of the keratinocytes density represented by system
(3) with the overestimate keratinocytes, mentioned in Theorem
1, which is used when the growth rate is assumed to be maximal.

keratinocytes population undergone a hyperproliferative nature and reach to a high density level (350 mm^{-3}).

Figure 2 shows the comparison of actual keratinocytes (seventh equation of system (3)) with the overestimated keratinocytes (described by Theorem 1). From this figure it is clear that the overestimated keratinocytes concentration reaches to stable condition after 50 days at density level about 350 mm^{-3}, this is almost same as the dynamical behavior of actual keratinocytes. In order to simulate the impulsive effect on keratinocytes, we have considered the keratinocytes dynamics (with no drug situation) as described by the seventh equation of system (3). In impulsive approach, it is mandatory that the population must be in equilibrium state; thus, for this approximation, the initiation of treatment policy will not be hampered [27].

In Fig. 3, we have demonstrated the qualitative behavior of keratinocytes for the cases: with and without impulse effect by considering different doses of Etanercept $(E_c = 0.002$ and $0.0002)$ when Fezakinumab is absent. This figure manifests that for the low dose of Etanercept, keratinocytes density is oscillating with small magnitude and chronologically decreasing towards the normal condition $(\tilde{K})$. Furthermore, for the high dose of Etanercept $(E_c = 0.002)$, keratinocytes density rapidly decreases and reaches to a density level below the desired threshold $(\tilde{K})$. The corresponding time-course of drug concentration also has been illustrated in Fig. 3. In absence of Fezakinumab, the dynamical behavior of keratinocytes and corresponding drug dynamics have been scrutinized for different dosing intervals of Etanercept $(\tau = 3$ and 6 days$)$ by considering the fixed dose $(E_c = 0.002$ (see Fig. 4). From these two Figs. 3

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and 4 it is clear that Etanercept (dose regime: $(E_c = 0.002$ $\tau = = 6$ days) alone is able to control the hyper-proliferation of keratinocytes after 20 days of treatment.

In Fig. 5, we have exposed the dynamical nature of keratinocytes for with and without impulse therapy by considering different dosages of Fezakinumab (F_c = 0.02, 0.002, and 0.0002) when Etanercept is absent. This figure exhibits that for any dose of Fezakinumab (low to high), keratinocytes density shows oscillating nature with very small magnitude. Though keratinocytes density is chronologically decreasing due to this inductive phase, but it not achieve the predefined healthy condition $(\tilde{K})$. The time-course of drug
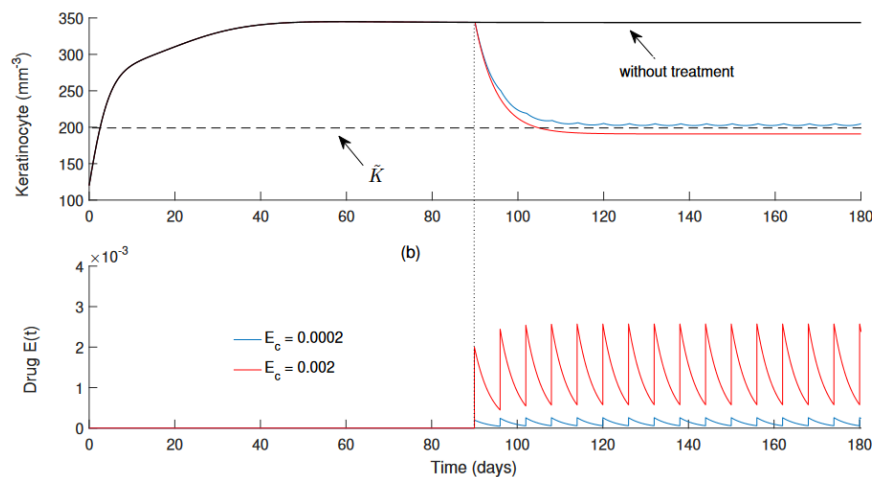

Figure 3.

In absence of Fezakinumab, concentration changes of keratinocytes with time and corresponding drug dynamics for different dosages of Etanercept (Ec), where the dosing interval (τ =6 days) is fixed. In order to simulate this figure, we have taken E50 =0.00001, and the rest of the parameter are taken from Table 1.

$$(\tilde{K}).$$

Figure 4.

In absence of Fezakinumab, keratinocytes dynamics for different dosing intervals of Etanercept (τ), where dose (Ec = 0.002) is fixed. In order to simulate this figure, we have taken E50 = 0.00001, and the other parameter values are taken from Table 1.

concentration by considering dosing interval . = 2 days has been illustrated in Fig. 3. For the different dosing intervals of Fezakinumab (. = 3 and 6 days), by considering the fixed dose *F.* = 0.002 the dynamical behavior of keratinocytes and corresponding drug dynamics have been plotted in Fig. 6. These two Figs. 5 and 6 show that Fezakinumab alone can only partially control the hyper-proliferation of keratinocytes.
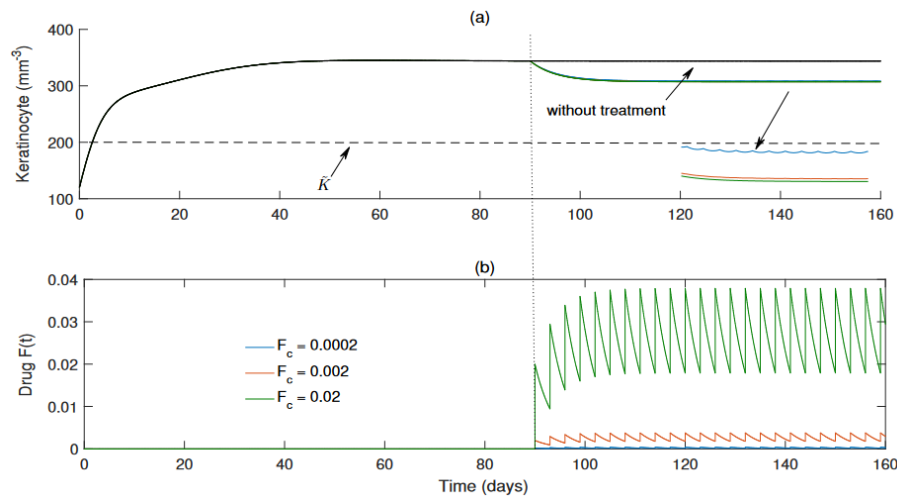
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Figure 5.

In absence of Etanercept, keratinocytes dynamics for different dosages (Fc) of Fezakinumab, where the dosing interval (σ =3 days) is fixed. In order to simulate this figure, we have taken F50 =0.00001, and the rest of the parameter are taken from Table 1.

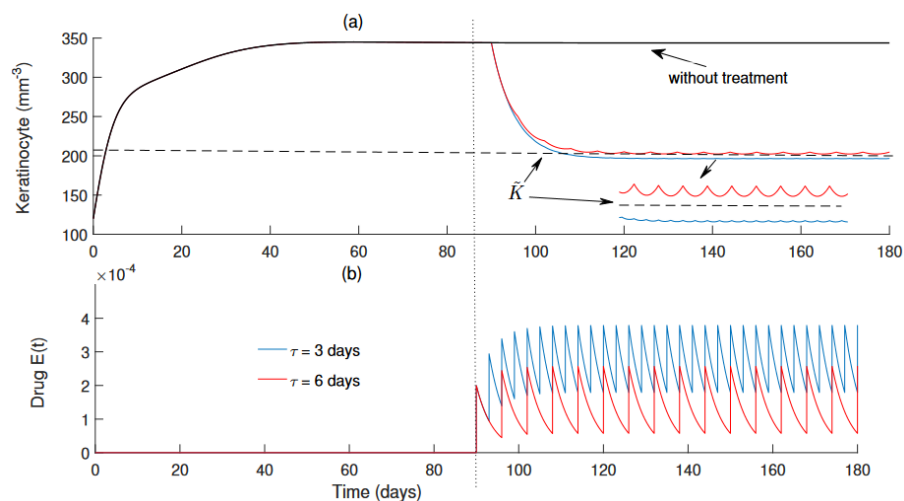**Figure 6.**

In absence of Etanercept, keratinocytes dynamics for different dosing intervals (σ) of Fezakinumab, where dose (Fc = 0.002) is fixed. In order to simulate this figure, we have taken E50 = 0.00001, and the other parameters are taken from Table 1.

The effect of combined biologic (Etanercept, Fezakinumab) on keratinocytes, taking dosing intervals $\tau = 6, \sigma = 4$ days and doses $(E_c = 0.002$ 0.0002, $F. = 0.0002, F_c = 0.0002$ has been illustrated in Fig. 7. This figure depicts that within 20 days of this combined impulse therapy keratinocytes decrease to the preferred density level $(\tilde{K})$. Single drug and the combined drug's levels have been provided in the corresponding drug dynamics.
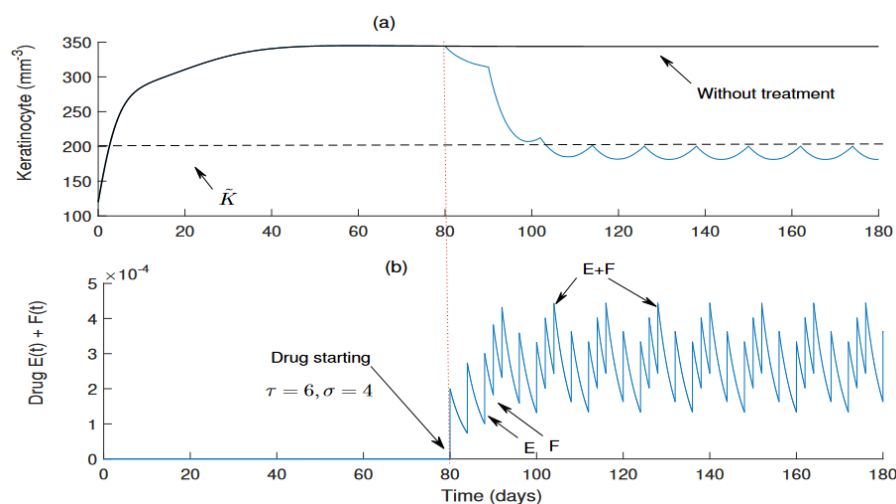
Figure 7.

The qualitative behaviour of keratinocytes dynamics in presence of both drug (Etanercept and Fezakinumab). In order to simulate this figure, we have taken E50 = 0.00001 and F50 = 0.00001. The rest of the parameter are taken from Table 1.

6 Conclusion

In this paper, formulating a mathematical model, we have studied the roles of different immune cells viz. Th_1, Th_2, Th_{17}, T_{reg}, and activated NK cells to encounter the hyperproliferation of keratinocytes during the disease progression. In absence of drugs, the proposed model system exhibits a unique steady state, namely, the coexistence equilibrium, which represents the psoriatic state. By using modified impulse theory we have also measured the efficacy and safety of Etanercept and Fezakinumab, which are applied as combined biologics. We have successfully demonstrated the effects of taking single drug and the combined drug by considering different dosing intervals for altered doses. The numerical simulations revel that high dose ($E_c = 0.002$) of Etanercept is able to clear the psoriatic lesions within 3 weeks. We have not found any suitable dose regime for Fezakinumab to maintain the normal keratinocytes level. On the other hand, our study shows that treatment with the low doses ($E_c, F_c = 0.0002$) of that combined biologics (Etanercept: 6 days interval and Fezakinumab: 4 days interval) may be an effective dosing schedule for the treatment of psoriasis. This study finally leads to the conclusion for short time treatment policy, instead of taking Etanercept with high dose for the entire length of the induction period, it would be better if the patient takes the drug combination (Etanercept and Fezakinumab) with low doses.

Due to the lack of sufficient primary data, we have chosen our parameter values to see the dynamical behaviors, namely, asymptotic stability, periodic oscillations, etc. Furthermore, the proposed treatment regime using Etanercept and Fezakinumab is based on hypothetical value of model parameters, but the result can be proposed for future

clinical trials. It is also possible to determine the therapy schedule for the similar combined drugs using the analytical and numerical techniques. Moreover, if proper data are obtained, a particular situation can be modeled, then we will be able to make these proposed results more applicable and biologically reasonable.

References

1. G, Birkhoff, G.-C, Rota, *Ordinary Differential Equations*, John Wiley & Sons, New York, 1978.

2. H.J, Bovenschen, P.C. van De Kerkhof, P.E. van Erp, R, Woestenenk, I, Joosten, H.J, Koenen, Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin, *J. Invest. Dermatol.*, 131(9):1853–1860, 2011.

3. Y, Cai, C, Fleming, J, Yan, New insights of T cells in the pathogenesis of psoriasis, *Cell. Mol. Immunol.*, 9(4):302–309, 2012.

4. A, Cline, G.J, Bartos, L.C, Strowd, S.R, Feldman, Biologic treatment options for pediatric psoriasis and atopic dermatitis, *Children*, 6(9):103, 2019.

5. P.K, Denman, D.L.S, McElwain, D.G, Harkin, Z, Upton, Mathematical modelling of aerosolised skin grafts incorporating keratinocyte clonal subtypes, *Bull. Math. Biol.*, 69(1):157–179, 2007.

6. E, Fitch, E, Harper, I, Skorcheva, S.E, Kurtz, A, Blauvelt, Pathophysiology of psoriasis: Recent advances on IL-23 and Th17 cytokines, *Curr. Rheumatol. Rep.*, 9(6):461–467, 2007.

7. E, Grigorieva, E, Khailov, Optimal strategies for psoriasis treatment, *Math. Comput. Appl.*, 23(3):45, 2018.

8. A, Hurwitz, On the conditions under which an equation has only roots with negative real parts, in R. Bellman, R. Kalaba (Eds.), *Selected Papers on Mathematical Trends in Control Theory*, Dover, New York, 1964, pp. 70–82.

9. K.E, Kester, J.F, Cummings, O, Ofori-Anyinam, C.F, Ockenhouse, U, Krzych, P, Moris, R. Schwenk, R.A, Nielsen, Z, Debebe, E, Pinelis, L. Juompan, J, Williams, M, Dowler, V.A, Stewart, R.A, Wirtz, M.-C, Dubois, M, Lievens, J, Cohen, W.R, Ballou, D.G, Heppner Jr, Randomized, double-blind, phase 2a trial of falciparum malaria vaccines RTS, S/AS01B and RTS, S/AS02A in malaria-naive adults: Safety, efficacy, and immunologic associates of protection, *J. Infect. Dis.*, 200(3):337–346, 2009.

10. E.N, Khailov, E.V, Grigorieva, On a third-order singular arc of optimal control in a minimization problem for a mathematical model of psoriasis treatment, *Proc. Steklov Inst. Math.*, 304(1):281–291, 2019.

11. I, Khanna, O, Kozicky, H, Fischer, Use of FDA-approved medications: Biologics for psoriatic arthritis in patients at an urban outpatient rheumatology clinic, *ACR Open Rheumatol.*, 1(9): 580–584, 2019.

12. M.V, Laptev, N.K, Nikulin, Numerical modeling of mutual synchronization of auto-oscillations of epidermal proliferative activity in lesions of psoriatic skin, *Biophysics*, 54(4):519, 2009.

13. G, Magombedze, S, Eda, V.V, Ganusov, Competition for antigen between Th1 and Th2 responses determines the timing of the immune response

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switch during Mycobaterium avium subspecies paratuberulosis infection in ruminants, *PLoS Comput. Biol.*, 10(1):e1003414, 2014.

14. P.J, Mease, A.J, Kivitz, F.X, Burch, E.L, Siegel, S.B, Cohen, P, Ory, D. Salonen, J. Rubenstein, J.T. Sharp, W. Tsuji, Etanercept treatment of psoriatic arthritis: Safety, efficacy, and effect on disease progression, *Arthritis Rheum.*, 50(7):2264–2272, 2004.

15. J, Meephansan, U, Subpayasarn, M, Komine, M, Ohtsuki, Pathogenic role of cytokines and effect of their inhibition in psoriasis, in A. Chiriac (Ed.), *An Interdisciplinary Approach to Psoriasis*, IntechOpen, London, 2017, p. 41, https://doi.org/10.5772/ intechopen.68421.

16. H.B, Oza, R, Pandey, D, Roper, Y, Al-Nuaimi, S.K, Spurgeon, M, Goodfellow, Modelling and finite-time stability analysis of psoriasis pathogenesis, *Int. J. Control*, 90(8):1664–1677, 2017.

17. A.S, Paller, E.C, Siegfried, R.G, Langley, A.B, Gottlieb, D, Pariser, I, Landells, A.A. Hebert, L.F. Eichenfield, V. Patel, K. Creamer, A. Jahreis, Etanercept treatment for children and adolescents with plaque psoriasis, *New Engl. J. Med.*, 358(3):241–251, 2008.

18. B, Perussia, The cytokine profile of resting and activated NK cells, *Methods*, 9(2):370–378, 1996.

19. T, Pinto-Almeida, T, Torres, Biologic therapy for psoriasis-still searching for the best target, *An. Bras. Dermatol.*, 89(2):365–367, 2014.

20. M, Rajagopalan, A, Mital, Biologics use in Indian psoriasis patients, *Indian Dermatol. Online J.*, 7(6):489, 2016.

21. K, Rønholt, L, Iversen, Old and new biological therapies for psoriasis, *Int. J. Mol. Sci.*, 18(11): 2297, 2017.

22. E.J, Routh, *A Treatise on the Stability of a Given State of Motion: Particularly Steady Motion*, Macmillan and Co, London, 1877.

23. A.K, Roy, F, Al Basir, P.K, Roy, A vivid cytokines interaction model on psoriasis with the effect of impulse biologic (TNF-. inhibitor) therapy, *J. Theor. Biol.*, 474:63–77, 2019.

24. A.K, Roy, P.K, Roy, Treatment of psoriasis by interleukin-10 through impulsive control strategy: A mathematical study, in P. Manchanda, R. Lozi, A. Siddiqi (Eds.), *Mathematical Modelling, Optimization, Analytic and Numerical Solutions*, Springer, Singapore, 2020, pp. 313–332.

25. A.K, Roy, P.K, Roy, E, Grigorieva, Mathematical insights on psoriasis regulation: Role of Th 1 and Th 2 cells, *Math. Biosci. Eng.*, 15(3):717, 2018.

26. P.K, Roy, A.K, Roy, E.N, Khailov, F, Al Basir, E.V, Grigorieva, A model of the optimal immunotherapy of psoriasis by introducing IL-10 and IL- 22 inhibitor, *J. Biol. Syst.*, 28(3):609– 639, 2020.

27. N.J, Savill, R, Weller, J.A, Sherratt, Mathematical modelling of nitric oxide regulation of rete peg formation in psoriasis, *J. Theor. Biol.*, 214(1):1–16, 2002.

28. K, Skak, K.S, Frederiksen, D, Lundsgaard, Interleukin-21 activates human natural killer cells and modulates their surface receptor expression, *Immunology*, 123(4):575–583, 2008.

29. R.J, Smith, L.M, Wahl, Distinct effects of protease and reverse transcriptase inhibition in an immunological model of HIV-1 infection with impulsive drug effects, *Bull. Math. Biol.*, 66(5): 1259–1283, 2004.

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30. A, Thomson, Etanercept in psoriasis: The evidence of its therapeutic impact, *Core Evidence*, 2(1):51, 2007.

31. A.-M, Tobin, B, Kirby, TNF-. inhibitors in the treatment of psoriasis and psoriatic arthritis, *BioDrugs*, 19(1):47–57, 2005.

32. A.M, Tobin, L, Lynch, B, Kirby, C, O'Farrelly, Natural killer cells in psoriasis, *J. Innate Immun.*, 3(4):403–410, 2011.

33. D, von Bubnoff, E, Andrès, F, Hentges, T, Bieber, T, Michel, J, Zimmer, Natural killer cells in atopic and autoimmune diseases of the skin, *J. Allergy Clin. Immunol.*, 125(1):60–68, 2010.

34. Y, Wu, Z, Tian, H, Wei, Developmental and functional control of natural killer cells by cytokines, *Front. Immunol.*, 8:930, 2017.

35. World malaria report 2015, World Health Organization, 2016.

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