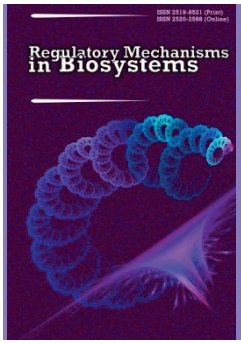

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Serum TNF-α and IL-10 levels during chronic carrageenan inflammation with thrombin inhibitor administration in rats

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Inflammatory cytokines are key mediators involved in the activation of the blood coagulation system, influencing various coagulation mechanisms, while activated coagulation proteases, physiological anticoagulants, and fibrinolytic system components can, conversely, modulate inflammation through specific cellular receptors. This study investigated the impact of the thrombin inhibitor dabigatran etexilate on a rat model of secondary chronic aseptic inflammation induced by an intramuscular injection of 10 mg of λ-carrageenan in 1 mL of isotonic saline into the right thigh of rats. Dabigatran etexilate was administered intragastrically via gavage at a dose of 15 mg/kg/day in 1 mL of isotonic saline daily for 28 days. Peripheral blood samples were collected on days 0, 1, 7, 14, 21, and 28 to determine serum TNF-α and IL-10 levels. During the natural course of secondary chronic carrageenan-induced inflammation, serum TNF-α levels increased until day 14 and subsequently decreased gradually towards day 28. Serum IL-10 levels during the natural course rose until day 21, followed by a slight drop on day 28. The administration of dabigatran etexilate modulated these cytokine dynamics, leading to a reduction in TNF-α levels compared to the natural course, particularly on days 14 and 21. Notably, IL-10 levels were significantly higher from day 1 to day 21 during dabigatran etexilate administration and exhibited a biphasic response, with a significant peak on day 7 and the highest levels observed on day 21. These distinct TNF-α and IL-10 level dynamics suggest a strong interaction between proinflammatory and anti-inflammatory processes. Dabigatran etexilate influenced the cytokine profile during chronic inflammation, potentially mitigating the inflammatory response as evidenced by the altered TNF-α and IL-10 levels. These findings highlight the potential of thrombin inhibitors, specifically dabigatran etexilate, in modulating inflammatory responses, warranting further investigation into its therapeutic mechanisms. Future research should focus on exploring the specific mechanisms through which dabigatran etexilate, and potentially other thrombin inhibitors, exert their anti-inflammatory effects, including their influence on humoral mediators relevant to the pathogenesis of chronic inflammation.

Keywords: secondary chronic inflammation; cytokines; dabigatran etexilate; blood serum; polysaccharide; between-subjects experiment.

Introduction

Inflammation is a complex biological protective response of the immune system to phlogogens, which can trigger acute and/or chronic inflammatory reactions in various organs, potentially leading to tissue damage (Chen et al., 2017). This process is designed to prevent further injury and initiate tissue repair processes by activating inflammatory signaling pathways and engaging a variety of immune cells, acute-phase proteins, and inflammatory mediators (Lawrence, 2009). Cytokines, small signaling proteins produced primarily by immune cells (e.g., monocytes, macrophages, T- and B-lymphocytes, dendritic cells, mast cells, NK cells, granulocytes) and some non-immune cells (e.g., fibroblasts, endothelial cells, Schwann cells, stromal cells, epithelial cells), play a central role in these processes (Zhang & An, 2007; Megha et al., 2021). Acting as chemical messengers, cytokines regulate diverse cellular functions, including proliferation, differentiation, apoptosis, immune cell activation and targeting to inflammation sites, and the release of other cytokines. Through complex networks of cell communications and interactions, they can also modulate or alter immune responses in specific cell populations (Zhang & An, 2007; Turner et al., 2014).

Cytokines are generally categorized into two groups based on their primary functions: proinflammatory cytokines, which initiate or promote inflammation (e.g., TNF-α), and anti-inflammatory cytokines, which suppress or resolve it (e.g., IL-10) (Zhang & An, 2007). Some cytokines, like IL-6, can exhibit both proinflammatory and anti-inflammatory effects depending on the site of synthesis and the context of the immune response, influenced by the state of inflammation, disease processes, and the tissues involved (Fontaine et al., 2016; Chen et al., 2019). There is crosstalk between proinflammatory and anti-inflammatory cytokines through negative feedback loops, whereby, under normal conditions, proinflammatory cytokines stimulate the production of anti-inflammatory cytokines to mitigate their potentially harmful effects and adverse reactions (Chen et al., 2019; Al-Qahtani et al., 2024). Proinflammatory cytokines are primarily produced by activated macrophages and are crucial in initiating and amplifying inflammatory responses by attracting leukocytes to the inflammation site to eliminate harmful agents (Zhang & An, 2007; Turner et al., 2014). However, excessive production of these cytokines and, as a result, excessive inflammation can lead to detrimental outcomes, including tissue damage, systemic metabolic disorders, systemic hemodynamic disorders, chronic and autoimmune diseases, organ failure or even multiple organ dysfunction, and eventually death (Iyer & Cheng, 2012; Czaja, 2014; Liu et al., 2016). Conversely, anti-inflammatory cytokines, primarily produced by activated lymphocytes and macrophages/monocytes, regulate the proinflammatory response to prevent uncontrolled or excessive immune activity, thus mitigating potential tissue damage (Opal & DePalo, 2000; Vidal et al., 2013; Carlini et al., 2023).

Inflammatory cytokines also play a key role in activating the coagulation system, influencing several of its mechanisms. Conversely, activated coagulation proteases, along with physiological anticoagulants and components of the fibrinolytic system, can modulate inflammation through specific cell receptors. The primary connections between inflammation and the coagulation system involve tissue factor (which is expressed on

the surface of endothelial cells and monocytes/macrophages in response to inflammatory cytokines), thrombin, the protein C system, and the fibrinolytic system. This intricate interplay between inflammation and the coagulation system is of immense importance in the pathogenesis of vascular diseases such as thrombosis and microvascular insufficiency (Levi & van der Poll, 2005). Natural anticoagulants help inhibit the increase in proinflammatory cytokine levels, minimize endothelial cell dysfunction and protect the endothelial barrier by reducing cellular susceptibility to inflammatory mediators, and facilitate the neutralization of certain inflammatory mediators. Therefore, reduced activity of natural anticoagulants not only promotes thrombosis but also exacerbates inflammation (Esmon, 2005). Conversely, inflammation reduces the activity of natural anticoagulants, disrupts the fibrinolytic system function, and initiates blood clotting (Levi & van der Poll, 2005).

A deeper understanding of the regulation of inflammatory cytokine pathways and the interplay between inflammation and the coagulation system is essential for improving the diagnosis and treatment of inflammatory diseases (Chen et al., 2017).

This study aimed to investigate the impact of administering the thrombin inhibitor dabigatran etexilate on the levels of proinflammatory cytokine TNF-α and anti-inflammatory cytokine IL-10 in peripheral blood serum during secondary chronic carrageenan inflammation in rats.

Materials and methods

Experimental animals. The study was conducted in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals: Eighth Edition (www.ncbi.nlm.nih.gov/books/NBK54050), the guidelines of Directive 2010/63/EU of the European Parliament and of the Council of Europe of 22 September 2010 on the protection of animals used for scientific purposes (https://eur-lex.europa.eu/eli/dir/2010/63/oj), the international bioethical standards of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, March 18, 1986, ETS No. 123), the General Ethical Principles for Experiments on Animals of the First National Congress on Bioethics (Kyiv, 2001), and the Arrive guidelines 2.0 (Simmonds, 2017; Percie du Sert et al., 2020).

In the experiment, we used the minimum number of animals necessary for statistical processing and obtaining reliable results (6 rats per group), as well as the minimum number of time points (days 0, 1, 7, 14, 21, 28) to achieve the aim and objectives of the study. The laboratory animals were kept in standard vivarium conditions: in separate metal cages, 6 rats per cage, on a normal diet with 24-hour free access to food and water, in a room with the following parameters: temperature of 22 ± 2 ºC, humidity of 45–50%, and a 12/12-hour light/dark cycle. The experimental animals were euthanized in accordance with the AVMA Guidelines for the Euthanasia of Animals: 2020 Edition (www.avma.org/resources-tools/avma-policies/avma-guidelines-euthanasia-animals) by decapitation under anesthesia with sodium thiopental (Brovapharma, Brovary, Ukraine), administered intraperitoneally at a dose of 40–50 mg/kg (Vogler, 2006). The study was conducted in compliance with Ukrainian legislation (Article 26 of the Law of Ukraine No. 3447-IV of February 21, 2006, "On the protection of animals from cruelty"), met international ethical requirements, and did not violate ethical standards in science or standards for conducting biomedical research. The Commission on Ethics and Bioethics of Kharkiv National Medical University approved the experimental study design at its 10th meeting on September 14, 2021 (Meeting Minutes No. 10 of September 14, 2021).

Experimental design. The research study was performed on 72 adult male WAG laboratory rats weighing 180–200 g (4 months old), which were raised in the vivarium of Kharkiv National Medical University. To exclude the influence of seasonal and daily fluctuations on the studied parameters, the study was conducted in the autumn-winter season.

The rats were randomly assigned into 2 control groups (6 rats each) and 2 experimental groups (30 rats each). The first control group consisted of intact rats without inflammation induction or drug administration, serving as the control for the natural course of inflammation – the intact control group. The second control group included rats that were administered the thrombin inhibitor without subsequent inflammation induction, serving as the control for dabigatran etexilate administration – the dabigatran control group. The first experimental group followed the natural course of secondary chronic carrageenan inflammation without drug administration, while the second experimental group was administered the thrombin inhibitor dabigatran etexilate in addition to inflammation induction. Each experimental group was also divided into subgroups of 6 rats for each time point (days 1, 7, 14, 21, and 28).

Secondary chronic aseptic inflammation was induced by an intramuscular injection of 10 mg of λ-carrageenan (cat. no. 22049, Sigma-Aldrich, Inc., St. Louis, MO, USA) in 1 mL of isotonic saline into the right thigh area (Radhakrishnan et al., 2003). A sterile 1 mL syringe with a 27G needle was used for each animal, and since the substance for injection was a gel, it was administered slowly over 10 seconds.

The thrombin inhibitor dabigatran etexilate (Boehringer Ingelheim Pharma GmbH & Co., Ingelheim am Rhein, Germany) was administered intragastrically via gavage at a dose of 15 mg/kg/day in 1 mL of isotonic saline, daily for 28 days (Dittmeier et al., 2016; Durmaz et al., 2022).

Material sampling and analysis. To ensure consistent sampling conditions, peripheral blood samples for TNF-α and IL-10 levels analysis were collected from each animal after euthanasia in the morning hours (09:00 AM – 11:00 AM). On day 0, samples were obtained from the control groups. The samples for the intact control group (no inflammation induction or drug administration) were taken immediately after the experiment began. Blood samples for the dabigatran control group were obtained one hour after administration of the thrombin inhibitor without inflammation induction (Ferreira et al., 2023). For the experimental groups (those undergoing inflammation induction), blood samples were subsequently collected on days 1, 7, 14, 21, and 28.

Blood sample analysis was performed using the Stat Fax 303 Plus Microstrip Reader (Awareness Technology, Inc., Palm City, FL, USA, 2011) with Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) Kits obtained from MyBioSource, Inc. (San Diego, CA, USA). The mouse/rat tumor necrosis factor alpha ELISA kit (cat. no. MBS2701339) and rat interleukin 10 ELISA kit (cat. no. MBS2700945) were used.

Statistical data analysis. Statistical analysis was conducted using R, version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria, 2024), within RStudio Desktop for Windows, version 2024.04.2 Build 764 (Posit Software, PBC, Boston, MA, USA, 2024). The following CRAN packages were utilized: "onewaytests" (version 3.0, 2023) for checking assumptions and conducting analysis of variance (ANOVA), "PMCMRplus" (version 1.9.10, 2023) for performing the Games–Howell test, "multcompView" (version 0.1-10, 2024) for generating a compact letter display, and "ggplot2" (version 3.5.1, 2024) for creating graphical plots.

The results of the data analysis are expressed as mean ± standard deviation (x ± SD) of 6 rats in every group. Data normality was assessed using the Shapiro–Wilk test, and heteroscedasticity was evaluated using Levene's test. Statistical significance for each time point was evaluated using one-way ANOVA. Post-hoc multiple pairwise comparisons were performed using the Games-Howell method (Lee & Lee, 2018; Sauder & DeMars, 2019). A compact letter display (CLD) was used to visually represent the results of the post-hoc test. Statistical significance was established at a P value threshold of less than 0.05.

Results

Tumor necrosis factor alpha dynamics during inflammation. During the natural course of secondary chronic carrageenan inflammation in rats, serum TNF-α levels exhibited a significant initial increase, reaching peak concentrations on day 14, followed by a gradual decline until day 28. These levels remained significantly elevated compared to the intact control group throughout the experiment (Table 1).

On day 1, TNF-α levels were 1.40-fold higher ($P = 1.7\times10^{-4}$) than those in the intact control group. By day 7, TNF-α levels had further increased, reaching a 3.72-fold elevation ($P = 1.3\times10^{-6}$) compared to the control group and a 2.65-fold increase ($P = 1.8\times10^{-5}$) compared to day 1. Peak TNF-α levels were observed on day 14, exhibiting a 9.49-fold increase ($P = 2.2\times10^{-16}$) compared to the control group and a 2.55-fold increase ($P = 1.3\times10^{-11}$) compared to day 7. While TNF-α levels de-

creased from day 14 to day 28, they remained significantly higher than those in the control group. On day 21, TNF-α levels were 5.49-fold higher ($P = 8.2\times10^{-9}$) than the control group but 0.58-fold lower ($P = 3.3\times10^{-10}$) than day 14. By day 28, TNF-α levels, while still 1.62-fold higher ($P = 9.2\times10^{-6}$) than the control group, were 0.29-fold lower ($P = 9.0\times10^{-7}$) than day 21.

Table 1
Serum levels of TNF-α (pg/mL) during secondary chronic carrageenan inflammation in rats (x ± SD, n = 6)

Time point	Natural course of the inflammation	Thrombin inhibitor administration
Control	49.47 ± 3.07^{i}	62.05 ± 0.95^{i}
Day 1	69.35 ± 0.73^{h}	54.62 ± 2.44^{j}
Day 7	183.98 ± 9.05^{d}	155.57 ± 5.64^{e}
Day 14	469.69 ± 8.46^{a}	386.36 ± 27.01^{b}
Day 21	271.83 ± 9.36^{c}	109.10 ± 11.39^{f}
Day 28	79.93 ± 0.85^{g}	53.14 ± 1.46^{j}

Note: different letters indicate values that are significantly different according to the Games-Howell test ($P < 0.05$).

Interleukin 10 dynamics during inflammation. Serum IL-10 levels also exhibited significant changes throughout the experiment during the natural course of inflammation, peaking on day 21 (Table 2). Except for day 1, IL-10 levels remained significantly higher than those of the control group.

Table 2
Serum levels of IL-10 (pg/mL) during secondary chronic carrageenan inflammation in rats (x ± SD, n = 6)

Time point	Natural course of the inflammation	Thrombin inhibitor administration
Control	4.97 ± 0.42^{cd}	3.39 ± 0.57^{g}
Day 1	4.01 ± 0.50^{fg}	11.18 ± 1.03^{bc}
Day 7	7.71 ± 0.44^{d}	20.33 ± 1.20^{a}
Day 14	9.27 ± 0.47^{c}	11.87 ± 1.08^{b}
Day 21	10.18 ± 0.77^{bc}	23.88 ± 2.45^{a}
Day 28	7.15 ± 0.62^{d}	5.81 ± 0.44^{e}

Note: see Table 1.

On day 1, IL-10 levels were 0.81-fold lower ($P = 0.108$) than those in the intact control group. By day 7, IL-10 levels increased and were 1.55-fold higher ($P = 2.2\times10^{-5}$) than the control group and 1.92-fold higher ($P = 3.9\times10^{-6}$) than day 1. On day 14, IL-10 levels were 1.87-fold higher ($P = 5.2\times10^{-7}$) than the control group and 1.20-fold higher ($P = 4.2\times10^{-3}$) than day 7. By day 21, the maximum IL-10 levels were observed, showing a 2.05-fold increase ($P = 2.0\times10^{-5}$) compared to the control group and a 1.10-fold increase ($P = 0.452$) compared to day 14. By day 28, IL-10 levels were 1.44-fold higher ($P = 1.7\times10^{-3}$) than the control group but 0.70-fold lower ($P = 8.0\times10^{-4}$) than day 21.

Effect of dabigatran etexilate on serum TNF-α levels. During secondary chronic carrageenan inflammation with the administration of the thrombin inhibitor dabigatran etexilate, the dynamics of TNF-α levels resembled those observed during the natural course of inflammation, with peak levels occurring on day 14 (Fig. 1).

On day 1, TNF-α levels during dabigatran etexilate administration were 0.88-fold lower ($P = 6.5\times10^{-3}$) than those in the dabigatran control group. By day 7, TNF-α levels were 2.51-fold higher ($P = 3.2\times10^{-6}$) than the control group and 2.85-fold higher ($P = 1.1\times10^{-7}$) than day 1. The highest TNF-α levels were observed on day 14, reaching a 6.23-fold increase ($P = 2.3\times10^{-5}$) compared to the dabigatran control group and a 2.48-fold increase ($P = 3.4\times10^{-5}$) compared to day 7. By day 21, TNF-α levels were 1.76-fold higher ($P = 2.5\times10^{-3}$) than the control group but 0.28-fold lower ($P = 1.8\times10^{-6}$) than day 14. By day 28, TNF-α levels were 0.86-fold lower ($P = 2.4\times10^{-5}$) than the dabigatran control group and 0.49-fold lower ($P = 0.001$) than day 21. Compared to the natural course of inflammation, dabigatran etexilate administration resulted in significantly lower TNF-α levels during all days of the experiment with decreases of 0.79-fold ($P = 1.9\times10^{-4}$) on day 1, 0.85-fold ($P = 3.9\times10^{-3}$) by day 7, 0.82-fold ($P = 0.007$) on day 14, 0.40-fold ($P = 3.5\times10^{-9}$) by day 21, and 0.60-fold ($P = 1.2\times10^{-8}$) on day 28.

Effect of dabigatran etexilate on serum IL-10 levels. In the case of IL-10 levels during inflammation with the administration of dabigatran etexilate, the levels fluctuated throughout the experiment, showing an initial peak on day 7 and a second, higher peak on day 21 (Fig. 2). On day 1, IL-10 levels during dabigatran etexilate administration were 3.30-fold higher ($P = 8.1\times10^{-6}$) than those in the dabigatran control group. From day 7 to day 21, IL-10 levels fluctuated. The first peak in IL-10 levels was observed on day 7, reaching a 6.00-fold increase ($P = 2.3\times10^{-7}$) compared to the control group and a 1.82-fold increase ($P = 2.6\times10^{-6}$) compared to day 1. By day 14, IL-10 levels were close to those observed on day 1, exhibiting a 3.50-fold increase ($P = 7.5\times10^{-6}$) compared to the dabigatran control group but a 0.59-fold decrease ($P = 5.8\times10^{-6}$) compared to day 7. On day 21, the second and highest peak in IL-10 levels occurred, reaching a 7.04-fold increase ($P = 3.4\times10^{-5}$) compared to the control group and a 2.01-fold increase ($P = 3.1\times10^{-4}$) compared to day 14. By day 28, IL-10 levels were 1.71-fold higher ($P = 4.2\times10^{-4}$) than the control group but 0.24-fold lower ($P = 1.0\times10^{-4}$) than day 21. Compared to the natural course of inflammation, dabigatran etexilate administration resulted in significantly different IL-10 levels, with increases of 2.79-fold ($P = 2.3\times10^{-5}$) on day 1, 2.64-fold ($P = 2.7\times10^{-6}$) by day 7, 1.28-fold ($P = 0.022$) on day 14, and a 2.35-fold increase ($P = 2.6\times10^{-4}$) by day 21, followed by a 0.81-fold decrease ($P = 0.046$) on day 28.

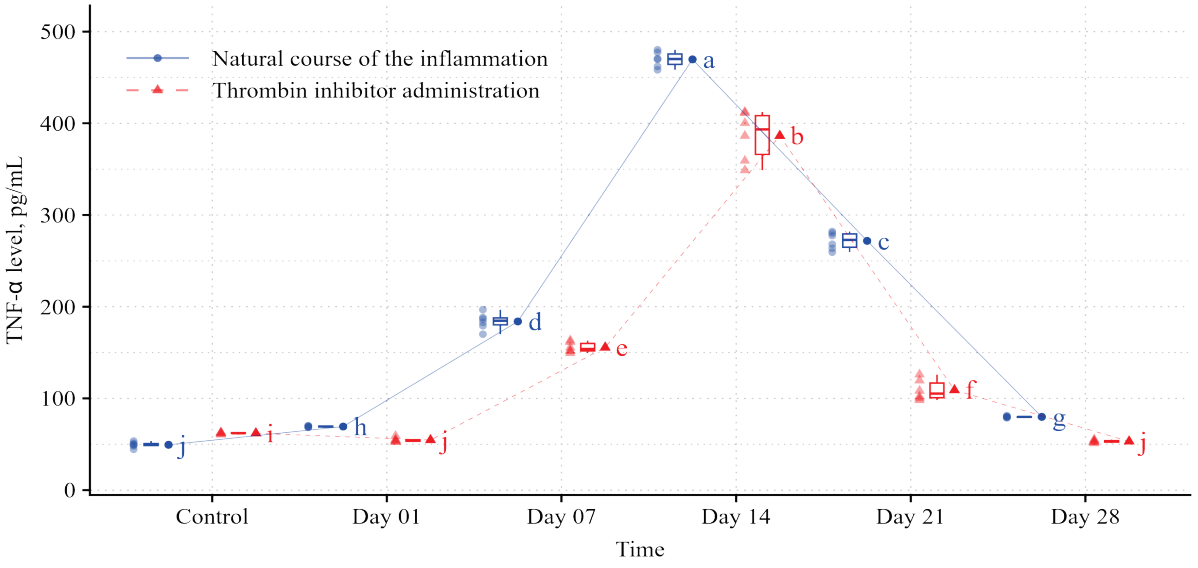

Fig. 1. Effect of dabigatran etexilate on serum TNF-α levels during secondary chronic carrageenan inflammation in rats: data are presented as individual values for each rat (multiple circles/triangles), box-and-whisker plot, mean value (single circle/triangle), and CLD; different letters indicate significant differences between groups (Games-Howell test, $P < 0.05$)

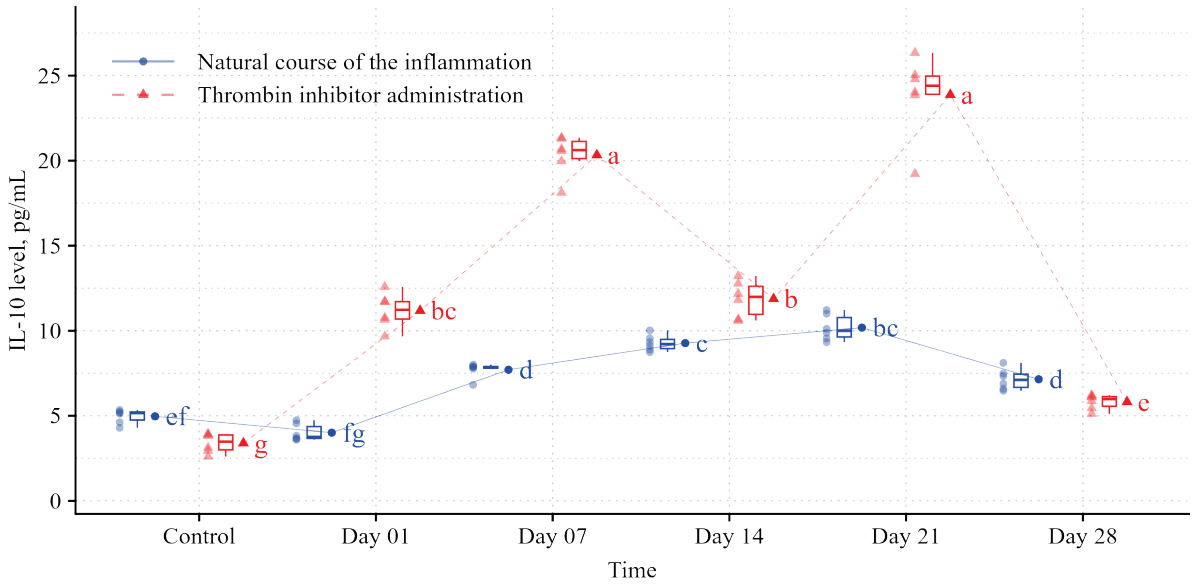

Fig. 2. Effect of dabigatran etexilate on serum IL-10 levels during secondary chronic carrageenan inflammation in rats: data are presented as individual values for each rat (multiple circles/triangles), box-and-whisker plot, mean value (single circle/triangle), and CLD; different letters indicate significant differences between groups (Games-Howell test, $P < 0.05$)

Discussion

TNF-α is one of the main proinflammatory cytokines that plays a central role in inflammatory reactions and acts as a pathological component of autoimmune diseases. By initiating signal transduction pathways through binding to its receptors, TNF-α influences subsequent cellular responses, including differentiation, proliferation, and survival (Jang et al., 2021). TNF-α-mediated signaling pathways play a key role in the pathogenesis of inflammatory diseases by aiding phagocytes in performing their protective functions during inflammation, such as the release of cytokines and the production of reactive oxygen species (Parameswaran & Patial, 2010; Zhao et al., 2021; Ben-Khemis et al., 2023).

IL-10 is one of the most potent anti-inflammatory cytokines and plays a critical role in modulating and regulating the immune response, inflammatory processes, and maintaining cellular homeostasis. IL-10 is essential in healing sterile wounds, preventing autoimmune diseases, inhibiting tumor progression, and reducing harmful inflammation in hyperinflammatory conditions (e.g., cancer, infectious diseases), thereby curbing disease progression (Iyer & Cheng, 2012; Saraiva et al., 2020; Carlini et al., 2023). IL-10 also strongly inhibits phagocyte activation (Moore et al., 2001). However, IL-10 administration alone has limited efficacy in patients with inflammatory diseases because TNF-α blocks the anti-inflammatory pathways of IL-10 in human monocytes, thus prolonging inflammation (Ben-Khemis et al., 2023).

Inflammation and coagulation are two of the body's main biological protective systems that play crucial roles in limiting tissue damage and in recognizing, containing, and eliminating invading pathogens (Wilhelm et al., 2023). The coagulation system and inflammation interact closely to optimize the organism's response to pathogen invasion, phlogogen exposure, or tissue damage. Inflammation can regulate the activation of blood coagulation, and the coagulation system can significantly influence inflammatory activity (Levi & van der Poll, 2005).

Overall, components of natural anticoagulant cascades inhibit the increase in cytokine levels. Components such as thrombomodulin reduce cellular sensitivity to inflammatory mediators and facilitate the neutralization of some of them, minimizing endothelial cell dysfunction and reducing the loss of endothelial barrier function (Esmon, 2005).

In the study by Durmaz et al. (2022), direct oral anticoagulants were shown to reduce oxidation and inflammation of renal tissue caused by aortic clamping. Dabigatran etexilate specifically reduced inflammation by decreasing levels of proinflammatory cytokines and oxidative stress in the kidneys. It has also been demonstrated that dabigatran etexilate can reduce ischemia-reperfusion histological damage in the kidneys, suggesting its potential to limit ischemia-reperfusion and distant tissue damage during acute ischemic clinical conditions. Another study by Ural et al. (2020) showed that dabigatran etexilate significantly improved tissue survival rates in skin degloving injuries in a rat tail model and helped limit the progression of ischemia and necrosis.

According to a study by Dittmeier et al. (2016), rats treated with dabigatran etexilate showed a significant reduction in infarct size without an increase in intracranial hemorrhage, and a significant recovery of neurological deficits compared to the control group. In this study, dabigatran etexilate administration reduced thrombin production and thrombosis, suppressed CD68 immunoreactivity, and decreased the expression of proinflammatory cytokines in the brain parenchyma. The permeability of the blood-brain barrier was not altered by dabigatran etexilate treatment. Therefore, prophylactic anticoagulation with the thrombin inhibitor dabigatran etexilate improves ischemic stroke outcomes by reducing thrombin-induced inflammation and thrombosis without increasing the risk of intracranial hemorrhage.

Conclusion

Research on secondary chronic carrageenan-induced inflammation in rats administered with the thrombin inhibitor dabigatran etexilate revealed distinct cytokine level patterns. The dynamics of serum TNF-α levels during dabigatran etexilate administration resembled those in the natural course of the inflammation, with an initial increase until day 14 followed by a decline. However, dabigatran etexilate administration significantly reduced TNF-α levels, particularly on days 14 and 21.

Conversely, IL-10 levels exhibited a different pattern, showing a biphasic response during the administration of dabigatran etexilate with a notable peak on day 7 and a maximum on day 21. These elevated serum IL-10 levels in rats administered dabigatran etexilate suggest an enhanced anti-inflammatory response, which may potentially contribute to the observed reduction in TNF-α levels.

The observed changes in serum TNF-α and IL-10 levels during dabigatran etexilate administration indicate a complex interplay between proinflammatory and anti-inflammatory processes. Furthermore, our findings demonstrate that the thrombin inhibitor dabigatran etexilate effectively modulates the inflammatory response, reducing inflammation intensity, and may offer therapeutic applications beyond its established anticoagulant properties.

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The authors declare no conflicts of interests.

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