Chapter

Platelets in Ulcerative Colitis: From Pathophysiology to Therapy

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Abstract

Based on the role of platelets in inflammation and hemostasis it has been assumed that antiplatelet therapy could be beneficial for patients suffering from ulcerative colitis. Platelets present a link between inflammation and coagulation. They have more than 300 active mediators stored in their granules. Upon activation, platelet degranulate and release a lot of microparticles and mediators and interact with other immune and non-immune cells thereby amplifying inflammation. The most important parameters of platelet activation are P-selectin and CD40 ligand expressed on their surface upon activation, and their soluble forms presented in blood. Today, we have potent anti-platelet drugs that can inhibit platelet activation and degranulation, and thereby reduce inflammation. The most important drugs are P2Y12 receptor antagonists such as ticagrelor and clopidogrel and glycoprotein IIbIIIa inhibitors. Ticagrelor is an active drug and besides antiplatelet activity, it has bactericidal activity against Gram-positive strains and *Clostridium difficile*. Clopidogrel is a prodrug with less anti-inflammatory effect than ticagrelor and no proven bactericidal activity. Glycoprotein IIbIIIa inhibitors are very potent in reducing platelet aggregation but have lower anti-inflammatory potential than ticagrelor and clopidogrel.

Keywords: ulcerative colitis, platelets, antiplatelet therapy, P-selectin, CD40 ligand, ticagrelor, clopidogrel, glycoprotein inhibitors

1. Introduction

Ulcerative colitis (UC) is a chronic disease resulting not only from the abnormal immune response but also from the activation of non-immune cells. Both, immune and non-immune cells are inducing inflammation that causes tissue injury [1, 2]. Platelets (Plt) are now recognized as proinflammatory cells, and aside from their primary role in a hemostasis they also enhance inflammation. The hypercoagulable state exists in the UC patients. Inflammation activates coagulation and coagulation amplifies inflammation [3, 4]. Platelets are unique cells without nucleus that have an important role in hemostasis and thrombosis, with a 5–9-day life span. Platelets have four granule types with stored numerous biologically active substances, such as platelet factor 4, fibrinogen, Von Willebrand factor (vWF), protein S, histamine, prostaglandin E2, platelet growth factor, thromboxane A2, transforming growth

factor-beta, coagulation factors, angiogenic and growth factors, β-thromboglobulin, P-selectin (Psel), chemokines, regulated upon activation, normal T cell expressed and presumably secreted (RANTES), monocyte chemotactic protein-1, interleukin (IL) 8 (IL-8), IL-1β, IL-7 [5, 6]. Platelets can interact with many different cells and contribute to vascular inflammation [7]. Platelet factor 4 and β-thromboglobulin are exclusively released from Plt and are increased in the serum of the patients with active UC [8]. Platelet activation is of utmost importance for Plt functioning and is a result of Plt interaction with numerous active molecules. The first step is adhesion to the subendothelial matrix. After that Plt change their shape, resulting in pseudopodia formation [9]. Platelet activation, in the UC patients, takes place in mesenteric microcirculation after exposure to subendothelial collagen, adenosine diphosphate (ADP), arachidonic acid, Plt activating factor, thrombin, fibrinogen, and cytokines from other cells. Upon Plt activation, they degranulate and release a lot of Plt-derived microparticles (PDMP) and preformed mediators and interact with other immune and non-immune cells [10]. The PDMP represent 70–90% of all human cell-derived microparticles and have high procoagulant (due to tissue factor) and proinflammatory potential [11]. They also secrete ADP which in turn bind to the P2Y1 and P2Y12 receptors on the membrane surface of the Plt and amplify initial Plt activation [12].

2. Mechanism of platelets intervention in ulcerative colitis

Upon activation, Plt express receptors on their surface, the most important being glycoprotein IIbIIIA (GPIIbIIIa), CD40 ligand (CD40L), Psel and receptors for cytokines, chemokines, and complement components [13]. A CD40L is a membrane protein, co-stimulatory molecule, presented mostly on the surface of the activated T lymphocyte (T Ly) and activated Plt. Its receptor is CD40, expressed on the surface of the immune cells, endothelial, epithelial cells, Plt, and other mesenchymal cells [14]. After Plt activation, CD40L and Psel are cleaved from the cell surface and secreted in the blood, being called soluble CD40L (sCD40L) and soluble Psel (sPsel). These soluble forms activate other cells, especially endothelial cells, fibroblasts, T Ly, monocyte, neutrophils, and B cells. The CD40/CD40L signaling pathway is a very important pathogenic mechanism in the UC, it amplifies inflammation and activates numerous immune and non-immune cells, including Plt [15, 16]. Platelets are the main source of sCD40L in UC. The number of CD40L positive T Ly and Plt is increased in colonic mucosa [17]. Also, the CD40L-CD40 signaling pathway is responsible for thromboembolic complications in UC patients and inflammation-induced angiogenesis. Platelet dysfunction exists in UC, meaning that Plt are becoming pro-inflammatory cells, and represent a connection between innate and adaptive immunity and between inflammation and coagulation [18].

3. Role of platelets as biomarkers in UC severity

P-selectin is expressed on the membrane surface of the activated Plt and endothelial cells. P-selectin has the most important function in leucocyte (Le) recruitment, mostly in the colonic mucosa [19]. The level of tissue expression of Psel is in strong positive correlation with the level of inflammation in colonic mucosa [20]. In severe inflammation, there is abundant Psel expression in colonic mucosa. Soluble Psel and sCD40L are excellent biomarkers of Plt activation [21].

Abnormalities seen in UC are: elevated Plt count (>450,000 × 10^9/L), reduction in mean Plt volume (MPV), increased platelet distribution width (PDW) value, increased plateletcrit value (PCT), increase in granular content, increased Plt activation and aggregation, hyperreactivity to agonist stimulation, such as ADP and collagen. These abnormalities are mediated by IL-6, are not seen in a healthy person, and are more pronounced in UC than in other inflammatory diseases like rheumatoid arthritis. The MPV and PCT show a negative correlation with disease activity [22–25]. Spontaneous platelet aggregation is observed in more than 30% of UC patients, a phenomenon that is not seen in healthy persons and rarely seen in other inflammatory disorders [26]. Histopathological studies found mesenteric vascular microthrombi to be the first finding in the mucosa of UC patients. Those microthrombi contribute to ischemia. Microthrombi are not found in mesenteric vessels in healthy persons [27]. Activated Plt form aggregates with Le and other Plt, so-called platelet-leukocyte aggregates (PLA) and Plt-Plt aggregates (PPA), via Psel [28]. Platelet-leukocyte aggregate number is increased in serum and colonic tissue of patients with active UC but does not correlate with disease activity, instead, there is a positive correlation with Plt number and serum sPsel concentration. But it is proven that Le within PLA are more active than free Ly or Plt [29]. Platelet-leukocyte aggregate react with endothelial cells, activate them, activate other free Plt and Le. Also, PLA activate endothelial cells more than free cells, leading to increased expression of adhesion molecules thus contributing to inflammation [30]. Increased Plt activation and aggregation, especially spontaneous platelet aggregation, are very much responsible for thrombosis and thromboembolic complications in UC, particularly arterial thrombosis [31, 32].

Platelet to Ly ratio, with cut off value of 175.9 (sensitivity 90.9%; specificity 78.4%; positive likelihood ratio 4.205, 95% confidence interval (95% CI) 2.214–7.894; area under the curve (AUC) 0.897, 95% CI 0.802–0.992) can serve as a biomarker for disease activity in UC, and can help us distinguish UC from healthy controls, that is, to identify UC patients with active disease [33].

We can also use neutrophil to Plt ratio to identify UC patients with active disease, with cut-off point of 14.94 (sensitivity 87.95%; specificity 63.5%) [34].

4. Antiplatelet drugs types

With the developments in medicine, especially pharmacology, we have a lot of antiplatelet drugs, and the number is constantly increasing [35]. The most important antiplatelet drugs are:

1. Thienopyridines represent a group of drugs that blocks ADP-mediated Plt aggregation by blocking the P2Y12 receptor on the Plt membrane surface. After Plt activation, ADP is released from Plt and then binds to P2Y12 on Plt surface and amplifies Plt activation, aggregation, degranulation, and procoagulant activity. Two thienopyridines are most important: clopidogrel and prasugrel. They are prodrugs and require biotransformation to become active. Clopidogrel is used for secondary stroke prevention and after coronary stenting (with aspirin). Prasugrel is used for the prevention of thrombosis after percutaneous coronary interventions [36].

2. Cyclopentyltriazolopyrimidines: ticagrelor. It is an active drug, with a fast onset of action, 30 minutes after ingestion, and it is a reversible P2Y12 receptor antagonist [37].

3. The ADP receptor antagonists: cangrelor. It has a short action time and it is used preoperatively in patients with atherosclerotic disease [38].

4. Aspirin or acetylsalicylic acid is the oldest antiplatelet drug that irreversibly inhibition both cyclooxygenase (COX) 1 and 2 and suppresses the production of prostaglandins and thromboxane. Other non-steroidal anti-inflammatory drugs inhibit COX-1 and Plt function, but their effect is short and reversible [39].

5. Phosphodiesterase inhibitors: dipyridamole that reversibly inactivates platelet cyclic adenosine monophosphate (cAMP)-phosphodiesterase thus increasing cAMP and decreasing Plt activity. Cilostazol is a selective inhibitor of phosphodiesterase type 3 leading to accumulation of cAMP and inhibition of Plt aggregation. It is used for treating peripheral vascular disease [40].

6. GP IIb/IIIa antagonists are anti-Plt agents that block binding GP IIb/IIIa to fibrinogen and inhibit Plt aggregation. Three agents are now being used: abciximab (monoclonal antibody), and two smaller molecule drugs tirofiban and eptifibatide [41].

7. Protease-activated receptor-1 (PAR-1) antagonists: a new class of drugs. Vorapaxar inhibits thrombin-related platelet aggregation [42].

They are used to prevent or treat arterial thrombosis.

The most important indications are: acute coronary syndrome, after the percutaneous coronary intervention (PCI) with stenting, acute ischemic stroke, after percutaneous intervention of peripheral arterial disease, stable angina, and primary prevention of coronary artery disease [43].

Not all anti-Plt agents are the same. Some of them affect mostly Plt aggregation, and some of them affect Plt aggregation and degranulation. The most significant contraindication for anti-Plt agents is active bleeding [44].

The most important antiplatelet drugs with the possibility to be used in UC are clopidogrel, ticagrelor, and GP inhibitors.

Clopidogrel is a prodrug, has 50% bioavailability. After biotransformation in the liver, its active metabolite binds to P2Y12 on the Plt surface and irreversibly inhibits ADP-mediated Plt aggregation and Plt activity. Due to the necessity of the liver biotransformation of clopidogrel by cytochrome P450 (CYP) enzymes CYP3A4/3A5, there is potential for drug interactions and therapeutic failure. Some genetic alterations in the CYP2C19 gene can lead to a low Plt response to clopidogrel [45].

Ticagrelor is an orally active drug. It is a reversible antagonist of P2Y12 receptor on surface Plt membrane that inhibits ADP induced Plt aggregation. It is given twice daily. After ingestion, maximal Plt inhibition was measured at 2–4 hours. It almost completely inhibits Plt aggregation. It has faster and more profound action on Plt inhibition than clopidogrel. Its half-life is 7 hours. After P2Y12 inhibition there is decreased Plt degranulation and decreased releasing of bioactive mediators from Plt, and low expression of Psel and CD40L on Plt surface. Ultimately it leads to reduced generation of PLA and PPA which is considered to be the major mechanism responsible for anti-inflammatory effect. It also inhibits the reuptake of adenosine which leads to its accumulation in the extracellular matrix. Major adverse events are bleeding, dyspnea and bradycardia [46].

Glycoprotein inhibitors compete with fibrinogen and VWF for binding to GPIIbIIIa, which represent the final step in Plt aggregation. They are very potent inhibitors of Plt aggregation. Three GP inhibitors are approved in clinical use: abciximab, eptifibatide, and tirofiban. The route of administration for all three drugs is intravenous. Major adverse events are bleeding and thrombocytopenia. They are very potent in inhibiting Plt aggregation but do not have a potent anti-inflammatory effect [47].

5. The role of antiplatelet drugs in the pathogenesis of UC

Antiplatelet therapy is not a part of standard therapy for treating UC patients, but growing evidence suggest that it is safe in UC and might be useful addition to the standard therapy. I will summarize published results.

This chapter is based on an evaluation of antiplatelet therapy in patients with UC. We defined key questions as our literature searching algorithm. We searched literature from PubMed according to the adequate MESH terms ("ulcerative colitis," "platelets," "antiplatelet therapy," "P-selectin," "CD40 ligand," "ticagrelor," "clopidogrel," and "glycoprotein inhibitors") for the period from 2000 to the present.

5.1 Antiplatelet agents'-ticagrelor and eptifibatide-safety in experimental colitis in mice

The authors conducted an animal study about the usage of antiplatelet agents—ticagrelor and eptifibatide in mice. Forty C57BL/6 mice (inbred females, age: 2–3 months, and average body mass: 20–24 g) were used. The bodyweight of mice was measured every day. Mice were observed for stool consistency and rectal bleeding on a daily basis so that disease activity index (DAI) could be calculated daily as the sum of the weight loss score, the diarrheal score, and the hematochezia score based on the method used by Friedman et al., as shown in **Table 1**. The DAI was used to assess the severity of colitis [48].

Colitis was induced in 30 mice by 5-day drinking water with 3.5% dextran sulfate sodium (DSS) (average molecular weight within the range of 35,000–55,000). All mice developed DSS colitis. After 5 days, DSS-induced mice were divided into three experimental groups, 10 each. The first (I) group, the DSS control group, received no intervention during the subsequent 5 days treatment period. The second (II) group, the ticagrelor treatment (PO) group, received 1 mg (in 0.5 mL) dosages per day of

	DAI score				
	0	**1**	**2**	**3**	**4**
Weight loss	0%	1–5%	6–10%	11–20%	>20%
Stoll consistency	Well-formed pellets		Semi-formed pellets		Liquid stools
Rectal bleeding	Hemoccult negative		Hemoccult positive		Gross bleeding

Table 1.
Disease activity index (DAI).

Brilinta® via gastric tube. The third (III) group, the eptifibatide treatment (IP) group, received 150 μg (in 0.2 mL) dosages per day of Integrilin® via intraperitoneal injection. Group of mice (n = 10), experimental control (K) group, received water without DSS during the 5 days period.

The primary outcome was bleeding, and the secondary outcomes were changes in platelet count, hemoglobin (Hgb) level, and hematocrit (HCT) level. Complete blood counts were determined for each group at baseline (day 0: before treatment; DSS1, PO1, and IP1 subgroups) and at 1 day after the last dose (day 5; DSS2, PO2, and IP2 subgroups). On day 5, all surviving mice were sacrificed, and an autopsy was performed. The Plt aggregation was measured using a multiplate Plt function analyzer with adenosine diphosphate and thrombin receptor-activating peptide.

Platelet aggregation was measured at baseline, after 2 h, and 24 h of ticagrelor and eptifibatide therapy. An autopsy showed signs of colitis and there was no evidence of recent bleeding in the liver, spleen, central nervous system, or serous cavities of any of the antiplatelet treatment groups. Histological findings of colonic mucosa in all three experimental groups after autopsy were that DSS2, PO2, and IP2 showed mild inflammation and ulceration.

Maximum weight loss was below 15% in all three experimental groups. Hematochezia was observed in all three experimental groups as blood around the anus and present in the sawdust or as hemoccult positive. Blood was seen from the fourth day of the experiment in all three experimental groups.

The DAI score was not significantly different between the three experimental groups (Kruskal-Wallis test; p = 0.925).

Significantly lower levels of Hgb and HCT were found in all three experimental groups (PO1, DSS1, PO1, and IP1 vs. control; Kruskal-Wallis test: p = 0.007 and p = 0.002, respectively) (**Figures 1** and **2**). However, the Plt count was not significantly different between any of the DSS groups and the control group (Kruskal-Wallis test: p = 0.640) (**Figure 3**). There were no significant differences in the drug-related changes in the Hgb, HCT, and Plt levels of the three DSS groups according to the two drugs administered (baseline vs. end of treatment; Kruskal-Wallis test: HGB, p = 0.369; HCT, p = 0.104; and Plt, p = 0.307) (**Figures 4–6**).

The authors concluded that administering eptifibatide and ticagrelor to DSS colitis mice did not cause serious adverse events. There was no significant decrease in Plt

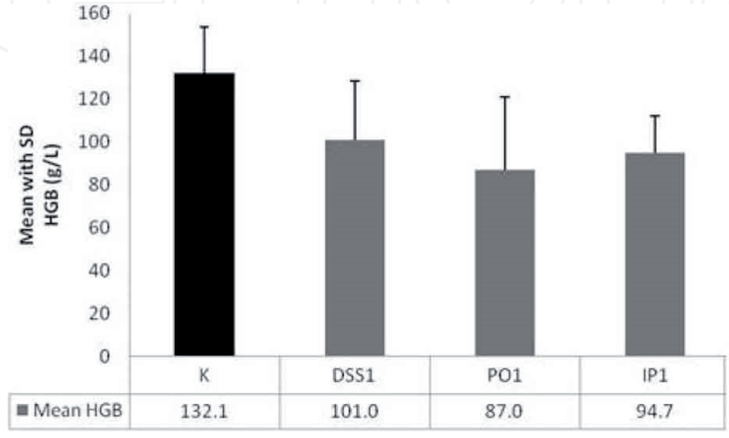

Figure 1.
Hemoglobin (Hgb) values before initiation of antiplatelet drug administration. Data are presented as mean ± SD. Groups DSS1, IP1, and PO1 represent DSS colitis mice before administration of drugs; K represents the experimental control group. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment.

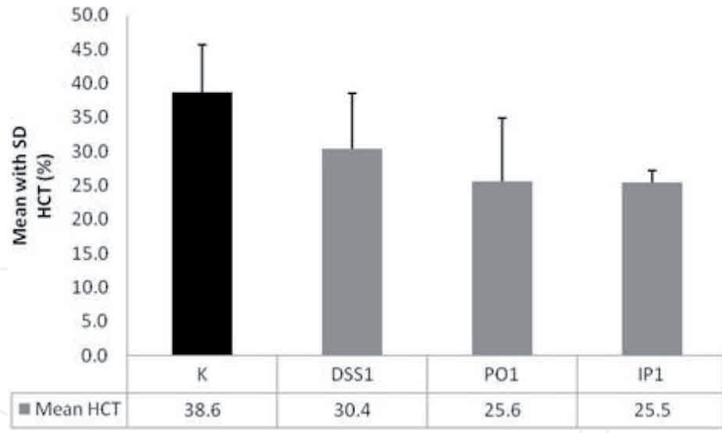

Figure 2.
Hematocrit (HCT) values before initiation of antiplatelet drug administration. Data are presented as mean ± SD. Groups DSS1, IP1, and PO1 represent DSS colitis mice before administration of drugs; K represents the experimental control group. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment (Kruskal-Wallis test: p = 0.002).

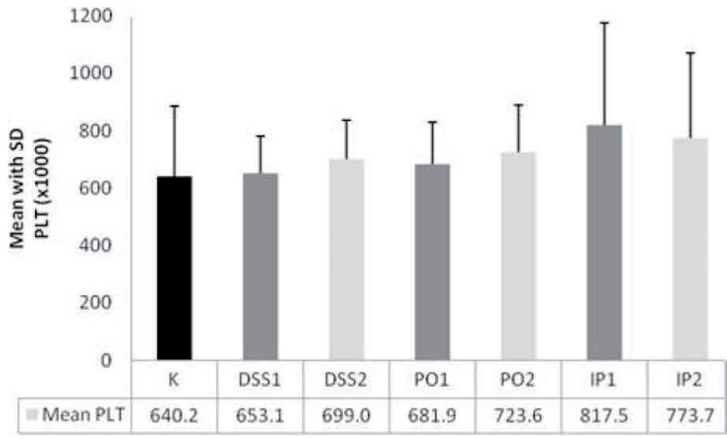

Figure 3.
Platelet (PLT) count for all groups. Data are presented as mean ± SD. Groups DSS1, IP1, and PO1 represent DSS colitis mice before administration of drugs; K represents the experimental control group. Groups DSS2, IP2, and PO2 represent DSS colitis mice after administration of drugs. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment (Kruskal-Wallis test: p = 0.640).

count or Hgb and HCT levels, and autopsy found no bleeding into the liver, spleen, serous cavities or intracranially. These observations support the potential use of antiplatelet therapy for treating UC in humans as an addition to the standard therapy. Ticagrelor could be used in the moderate form of UC and eptifibatide in the severe form, together with standard therapy.

5.2 Evaluation of anti-inflammatory effect of anti-platelet agent-clopidogrel in experimentally induced inflammatory bowel disease

The goal of this research was to evaluate the anti-inflammatory effect of clopidogrel on an animal model for Crohn's disease (TNBS model) and ulcerative colitis (oxazolone induced) in rats. Rats were weighing 150–200 g and were housed in standard conditions, on a standard diet and water ad libitum. Ulcerative colitis was induced by intrarectal administration of oxazolone on first day. Rats were divided into four groups, each consisting of six animals: **Control** group (healthy rats),

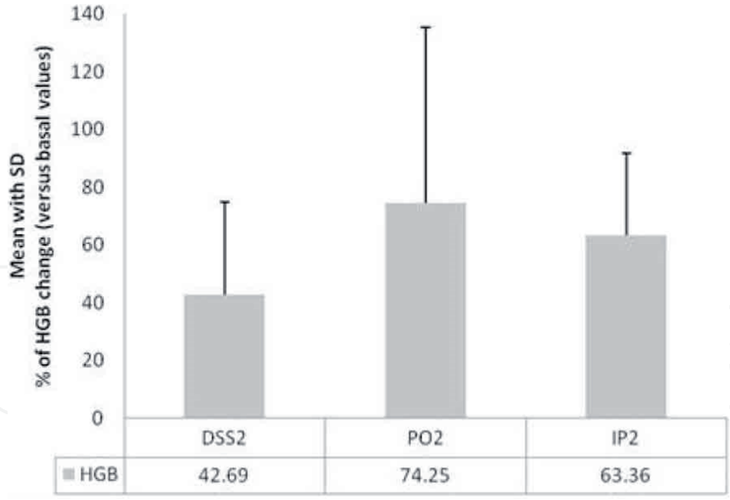

Figure 4.
Percent change in values of hemoglobin (Hgb) relative to basal values. Groups DSS2, IP2, and PO2 represent DSS colitis mice after administration of drugs. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment (Kruskal-Wallis test: HGB, p = 0.369).

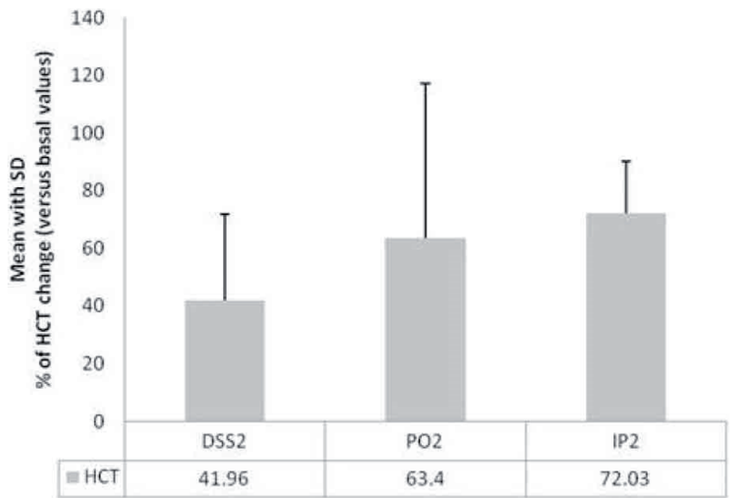

Figure 5.
Percent change in values of hematocrit (HCT) relative to basal values. Groups DSS2, IP2, and PO2 represent DSS colitis mice after administration of drugs. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment (Kruskal-Wallis test: HCT, p = 0.104).

Oxazolone group (induced UC without treatment), **Standard** group (oxazolone + sulfasalazine for the next 21 days), and **Test** group (oxazolone + clopidogrel per os for the next 21 days). At regular time intervals percentage change in body weight, colon mucosal damage index (CMDI), DAI, and myeloperoxidase (MPO) activity were measured. The CMDI, DAI, and MPO were used to assess inflammatory changes in colonic mucosa. It was shown that the test group resolved symptoms and significantly reduced MPO activity, DAI, and CMDI, better than other groups [49].

5.3 Acetylsalicylic acid reduces the severity of dextran sodium sulfate-induced colitis and increases the formation of anti-inflammatory lipid mediators

The goal of this study was to evaluate the effect of acetylsalicylic acid (ASA) on DSS colitis in mice. Female C57BL/6 mice, average body weight 19–21 g, were divided into three groups: **Control group**, **another group** receiving 3% DSS and no treatment

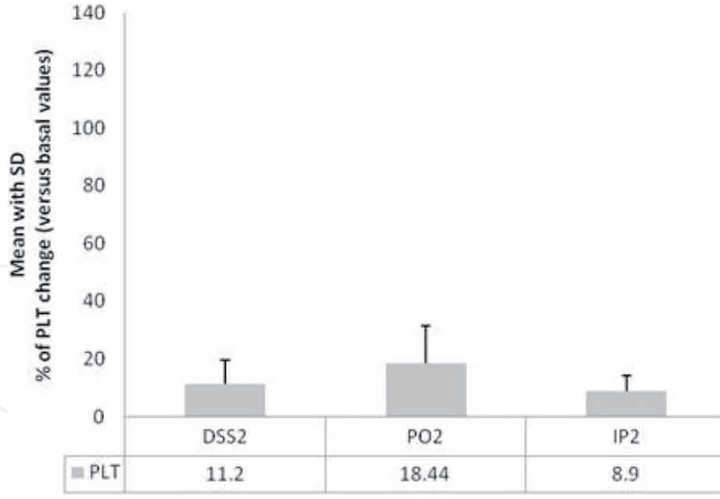

Figure 6.
Percent change in values of platelets (PLT) relative to basal values. Groups DSS2, IP2, and PO2 represent DSS colitis mice after administration of drugs. DSS, dextran sulfate sodium; IP, eptifibatide treatment; PO, ticagrelor treatment (Kruskal-Wallis test: PLT, p = 0.307).

and **ASA** group, receiving 3% DSS and daily intraperitoneal ASA for 5 days. Bodyweight, occult blood in stool samples, histological evaluation of the distal colon, and magnetic resonance imaging (MRI) were measured to evaluate colitis severity. The authors concluded that DSS colitis can be alleviated by ASA [50].

5.4 CD40-CD40 ligand mediates the recruitment of leukocytes and platelets in the inflamed murine colon

The aim of this study was to evaluate the role of the CD40-CD40L signaling pathway in intestinal inflammation in DSS colitis in mice and the anti-inflammatory effect of Trapidil (triazolopyrimidine) on intestinal inflammation. Trapidil is an antagonist of platelet-derived growth factor and it was developed to inhibit the response of monocytes to CD40L. They found a 10-fold increase in CD40 expression in endothelial cells in the colon (an important result of CD40-CD40L signaling pathway), increased recruitment of Plt and leukocytes in colonic venules due to CD40-CD40L pathway and significant inhibition of CD40-CD40L signaling pathway with Trapidil [51].

5.5 The role of P-selectin in experimental colitis as determined by antibody immunoblockade and genetically deficient mice

The objective of this study was to evaluate the role of Psel on leukocyte recruitment and the effect of its blockade with an anti-P-sel antibody. They induced DSS colitis in wild type and P-selectin−/− C57BL/6 J mice. Disease activity index, plasma IL-6, length of colon and rectum, histological damage of the colon, and MPO activity of the distal colon were evaluated. Leukocyte-endothelial interaction in colonic venules was assessed using intravital microscopy. Vascular cell adhesion protein 1 (VCAM-1) and intercellular adhesion molecule 1 expression on endothelial cells and expression of very large antigen-4 integrin on circulating leukocytes were obtained. They found that Psel has an important role in intestinal inflammation in DSS colitis. Its blockade or genetic deficiency offers protection against DSS colitis. They also found that treatment of DSS colitis with Psel antibody was very potent in reducing

DAI, MPO activity, and leukocyte adhesion. The VCAM-1 over-expression in the colon and extracolonic organs and increased level of IL-6 in circulation were observed in P-selectin−/− mice, but not in mice treated with anti-P-sel antibodies. The conclusion was that Psel is a key molecule for the development of DSS colitis and that Psel antibodies administration or genetic deficiency offers protection against DSS colitis by diminishing leukocyte recruitment in the colon [52].

5.6 Daily aspirin use does not impact clinical outcomes in patients with inflammatory bowel disease

It was a retrospective analysis of 174 patients with pre-existing inflammatory bowel disease, who were taking aspirin, due to cardiac comorbidity, for at least 18 months and did not differ in age, gender, disease duration, smoking status, medication usage, or baseline C-reactive protein. They were looking for the connection between aspirin and inflammatory bowel disease (IBD) related hospitalization/surgery/corticosteroid required during the period of follow-up. Their results indicate that aspirin use did not have a clinical impact on IBD patients [53].

6. The role of antiplatelet drugs in the treatment of UC

A retrospective analysis of 36 patients with pre-existing IBD (test group), who started on combination therapy of aspirin and clopidogrel for at least 6 months, due to PCI for coronary artery disease. There was a control group with IBD matched for gender and age, not taking antiplatelet therapy. They found no change in frequency of IBD exacerbations between groups, after the initiation of the aspirin and clopidogrel in the test group [54].

6.1 Antibacterial activity of ticagrelor in conventional antiplatelet dosages against antibiotic-resistant Gram-positive bacteria

After analysis of the PLATO study, the question was raised whether ticagrelor has antibacterial activity in standard anti Plt dosages against Gram-positive bacteria because patients treated with ticagrelor had a lower risk of infection-related death than patients treated with clopidogrel. Authors proved that in vitro ticagrelor has bactericidal activity against all Gram-positive strains tested, including drug-resistant strains glycopeptide intermediate *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, methicillin-resistant *S. aureus*, and vancomycin-resistant *Enterococcus faecalis*. These bactericidal concentrations are not reached in the systemic circulation but might be reached at the infection site probably by drug accumulation [55].

6.2 Repurposing a platelet aggregation inhibitor ticagrelor as an antimicrobial against Clostridioides difficile

The author tested the antimicrobial activity of ticagrelor against different types of *Clostridium difficile* (C. diff) in vitro. They found that ticagrelor has minimal inhibitory concentration (MIC) 20–40 μg/ml for all types of C. diff. Ticagrelor had a more rapid killing profile compared to metronidazole and vancomycin, and also inhibited biofilm formation, which is very important for the pathogenicity of C. diff infection.

Ticagrelor effectively reduced spore germination of C. diff, caused membrane disruption in C. diff and had an additive effect on metronidazole and vancomycin [56].

7. Conclusion

The exact pathophysiology of ulcerative colitis is unknown. Except immune cells, it is important to take platelet function into the consideration so we could improve the response rate to the standard therapy in ulcerative colitis patients. Antiplatelet therapy is still not a part of the therapeutic armamentarium for this disease. We have increasing evidence that raises the possibility of using antiplatelet therapy in humans with ulcerative colitis. Antiplatelet therapy in UC is safe and it seems that ticagrelor could be the drug of the first choice.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

ASA	acetylsalicylic acid
ADP	adenosine diphosphate
AUC	area under the curve
CD40L	CD40 ligand
C. diff	*Clostridium difficile*
CMDI	colon mucosal damage index
cAMP	cyclic adenosine monophosphate
COX	cyclooxygenase
CYP	cytochrome P450
DSS	dextran sulfate sodium
DAI	disease activity index
GPIIbIIIa	glycoprotein IIbIIIA
HCT	hematocrit
Hgb	hemoglobin
IBD	inflammatory bowel disease
IL	interleukin
Le	leucocyte
MRI	magnetic resonance imaging
MPV	mean Plt volume
MIC	minimal inhibitory concentration
MPO	myeloperoxidase
PCT	plateletcrit
PCI	percutaneous coronary intervention
PDW	platelet distribution width
PLA	platelet-leukocyte aggregates
Plt	platelets
Psel	P-selectin
PDMP	Plt derived microparticles

PPA	Plt-Plt aggregates
PAR-1	protease-activated receptor-1
RANTES	regulated upon activation, normal T cell expressed and presumably secreted
sCD40L	soluble CD40L
sPsel	soluble Psel
T Ly	T lymphocyte
UC	ulcerative colitis
VCAM-1	vascular cell adhesion protein 1
vWF	Von Willebrand factor
95% CI	95% confidence interval

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