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Review

Immunomodulatory properties of cimetidine: Its therapeutic potentials for treatment of immune-related diseases

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ABSTRACT

Histamine exerts potent modulatory impacts on the cells of innate- [including neutrophils, monocytes, macrophages, dendritic cells (DCs), natural killer (NK) cells and NKT cells] and adaptive immunity (such as Th1-, Th2-, Th17-, regulatory T-, $CD8^+$ cytotoxic T cells, and B cells) through binding to histamine receptor 2 (H2R). Cimetidine, as an H2R antagonist, reverses the histamine-mediated immunosuppression, as it has powerful stimulatory effects on the effector functions of neutrophils, monocytes, macrophages, DCs, NK cells, NKT cells, Th1-, Th2-, Th17-, and $CD8^+$ cytotoxic T cells. However, cimetidine reduces the regulatory/suppressor T cell-mediated immunosuppression. Experimentally, cimetidine potentiate some immunologic activities in vitro and in vivo. The therapeutic potentials of cimetidine as an immunomodulatory agent were also investigated in a number of human diseases (such as cancers, viral warts, allergic disorders, burn, and bone resorption) and vaccination. This review aimed to provide a concise summary regarding the impacts of cimetidine on the immune system and highlight the cellular mechanisms of action and the immunomodulatory effects of this drug in various diseases to give novel insights regarding the therapeutic potentials of this drug for treatment of immune-related disorders. The review encourages more investigations to consider the immunomodulatory characteristic of cimetidine for managing of immune-related disorders.

1. Introduction

Histamine is generated by innate and adaptive immune cells via decarboxylation of the amino acid L-histidine by the enzyme histidine decarboxylase [1]. The basophils and mast cells are known as the main sources of histamine [2,3]. In addition, histamine is released by other cells such as dendritic cells (DCs), macrophages, epithelial cells, neutrophils, platelets and gastric enterochromaffin-like cells [2,3]. Histamine influences the cells of both innate and adaptive immune systems [1]. Distinct immunoregulatory impacts of histamine are exerted through binding to the four subtypes of histamine receptors [1,4].

The histamine receptor 2 (H2R) is expressed on the parietal gastric cells, muscle cells, epithelial cells, endothelial cells, neuronal cells, hepatocyte neutrophils, eosinophils, basophils, mast cells, monocytes, macrophages, DCs, T cells and B cells [1]. The signaling through H1R activates phospholipase C and protein kinase C which induces certain transcription factors, whereas the signal transduction from H2R lead to the induction of adenylyl cyclase, which enhances the amounts of cyclic adenosine monophosphate (cAMP) and activates the protein kinase A (PKA) [1,4]. The signaling from H3R and H4R exert preventive impacts effects on the H2R-related pathways [1]. Therefore, histamine may perform different activities according to its target cell type and the receptor type. For example, the binding of histamine to H1R on DCs reinforces the Th1 cell polarization, while the H2R activation inhibits both Th1 cell- and Th2 cell-related responses, but promotes the Treg cell activities [2]. The H2R activation regulates innate and adaptive

Abbreviations: DTH, delayed-type hypersensitivity; FDA, Food and Drug Administration; FOXP3, forkhead box P3; H2R, histamine receptor 2; HBsAg, hepatitis B surface antigen; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NKT, natural killer T cells; OPG, osteoprotegerin; PBMCs, peripheral blood mononuclear cells; RANK, receptor activator of nuclear factor κB; RANKL, RANK ligand; ROP2, rhoptry protein 2; SRBC, sheep red blood cell; TLR, toll like receptor; VEGF, vascular endothelial growth factor

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immune responses, including mast cell degranulation, DC responses, T cell proliferation, Th1 cell-derived cytokine and antibody production by B cells [5].

Cimetidine, as an H2R antagonist, was approved in the USA by the FDA to reduce gastric acid secretion, and improve gastric ulcer in 1979 [6]. The immunopotentiating impacts of cimetidine have been also indicated in many researches from about 40 years ago [7]. Cimetidine exerts powerful immunomodulatory effects on the effector functions of the innate and adaptive immune system.

This review aimed to provide a concise summary concerning the cimetidine effects on immune responses and highlight the cellular mechanisms of action and the immunomodulatory effects of this drug in various diseases to give novel insights regarding the therapeutic potentials of this drug for treatment of immune-related disorders. The review encourages more investigations to consider the immunomodulatory properties of cimetidine for managing of immune-related disorders and provide a new direction for subsequent researches and the other clinical applications of this drug.

2. The effects of cimetidine on the innate immunity

Histamine exerts different influences on the monocyte- or macrophage-mediated inflammatory responses. Histamine stimulates the monocytes to express the monocyte chemoattractant protein (MCP)-1 and its receptors CCR2 via binding to H2R [2]. However, histamine inhibits the chemotaxis, phagocytosis, TNF-α, IL-12 and superoxide anion generation in macrophages via H2R activation [2]. Histamine also inhibits the NADPH oxidase activity that plays a principle role in reactive oxygen species (ROS) formation by monocytes and macrophages via H2R triggering [8]. The IL-27 secretion by human monocytes is down-regulated by histamine through H2R induction, but it has no effect on the IL-6, IL-10 and TNF-α production [2,9]. Further, histamine inhibits the CXCL10, IL-12, and TNF-α production in human monocyte-derived DCs through H2R induction [1].

In one study, the human monocytes were cultured with IL-4 and GM-CSF in presence or absence of histamine. It was found that the presence of histamine lead to the generation of $CD1a^{-}CD14^{+}$ DCs with high phagocytic activity and cytokine-producing capacity, but low allostimulatory capability compared with $CD1a^{+}CD14^{-}$ DCs. The suppressive effects of histamine on $CD1a^{+}$ $CD14^{-}$ DC differentiation were disrupted by cimetidine, an H2R antagonist [10]. The number of circulating $H2R^{+}$ monocytes is also significantly reduced in patients with inflammatory bowel disease (IBD). Histamine efficiently suppresses the toll like receptor (TLR)-mediated cytokine expression by PBMCs isolated from healthy individuals but not in PBMCs obtained from patients with IBD [4].

Histamine suppresses the leukotriene generation in human neutrophils via binding to H2R [1]. Histamine also inhibits human neutrophil chemotaxis and T-lymphocyte proliferation via H2R induction. The mentioned effects are reversed by cimetidine [11]. The topical cimetidine oral rinse also promotes the neutrophil-mediated antibacterial functions (such as chemotaxis, superoxide production, and ultimately phagocytosis and bacterial killing) in the gingival crevice by overriding the suppressive effects of histamine through competing for binding to H2R [12]. However, the results from a study were indicated that cimetidine did not influence the neutrophil chemotaxis or phagocytosis [13].

The immunomodulatory impacts of cimetidine were summarized in the Fig. 1. The cimetidine administration to the healthy adult individuals enhance the blood leukocyte counts, increase the blood neutrophil counts, increase the blood number of $CD3^{+}$ and $CD4^{+}$ T lymphocytes. However, the counts of natural killer (NK) cells and NKT cell subpopulation was not affected [14]. In an animal model of hepatocellular carcinomas, it has been found that cimetidine treatment enhance the NK cell activity in splenic lymphocytes [15]. However, the number of splenic NK cells was not influenced by cimetidine administration [15]. The considerable NK cell-mediated cytotoxicity against target K562 cells were also reported in cimetidine-treated PBMCs [16].

IL-18, a monocyte/macrophages-derived cytokine which is matured by caspase-1, enhances the local antitumor immune responses through activating NK cells and $CD8^{+}$ cytotoxic T cells (CTLs) [17]. IL-18 also reduces tumor development through inhibition of angiogenesis and induction of apoptosis in tumor cells [17]. It was found that cimetidine activates caspase-1, which convert the immature IL-18 to mature/active IL-18. Further, the impacts of cimetidine on IL-18 expression are reproduced in PBMCs from wild type healthy mice, but not in PBMCs from H2R-deficient mice [18].

The lipid-stimulated invariant natural killer T (iNKT cell) cells from H2R-deficient mice secrete higher amount of IL-4, IL-5, and GM-CSF compared with cells from wild type healthy mice [19]. Therefore, H2R induction may reduce iNKT cell activity and cimetidine has the capability to improve the iNKT cell activity. The in vivo administration of lipid antigens to the lung of H2R-deficient mice causes larger mucus secretion, higher inflammatory cell recruitment, and higher cytokine production compare to wild type mice [19].

It is worth noting that cimetidine may display anti-inflammatory properties to overcome the harmful inflammatory responses. For example, it has been reported that cimetidine reduces the $O2^{-}$ or H2O2 formation by neutrophils in a dose-dependent manner [13]. Cimetidine also suppresses the high glucose levels-mediated expression of adhesion molecules (such as ICAM-1 and P-selectin) on the surface of endothelial cells and prevents the neutrophil adhesion to endothelial cell [20]. Reducing impacts of cimetidine on the neutrophil–endothelial cell interaction represent that cimetidine may also consider as an anti-inflammatory agent [20].

Collectively, the results from the aforementioned studies represent that histamine has profound suppressive influences on the various elements of the innate immunity through induction of H2R. The mentioned suppressive effects of histamine may be interrupted using cimetidine as an H2R antagonist.

3. The effects of cimetidine on the adaptive immune responses

3.1. The effects of cimetidine on the antigen presenting cells (APCs)

The APC-derived IL-12 stimulates the Th1 cell-mediated immune response, whereas IL-10 lead to the maturation of DCs into a phenotype which induces Treg- and Th2 cell-related immune response [21]. Histamine efficiently inhibits the IL-12 secretion, while induces the IL-10 expression by human monocytes through H2R activation [21]. Histamine also increases the IL-10 production, whereas reduces the IL-12 expression in DCs via H2R induction [22]. Further, histamine promotes the IL-10 production, but inhibits the IL-12 expression in LPS-induced DCs [23]. Therefore, the histamine-exposed DCs induce the polarization of the native $CD4^{+}$ T cells toward effector Th2- and Treg cells. The histidine decarboxylase-deficient mice, which are not genetically able to produce histamine, display predominantly a DC-related cytokine profile causing Th1 cell differentiation [24]. Histamine increases the chemokines CCL17 and CCL22 production, while decreases the CXCL10 expression in DCs through H2R induction [25]. CCL17 and CCL22 act as chemoattractant agents for Th2 cells [26]. These observations represent the histamine mediates a shift in Th1/Th2 cell balance toward Th2 cell domination.

As it is expected, that cimetidine is capable to reverse the impacts of histamine on the expression of IL-2, IL-10 and IL-12 by PBMCs [21,27]. Moreover, cimetidine inhibits the histamine-mediated increasing of the IL-10 production, but improves the histamine-mediated reduction of IL-12 secretion by LPS-induced DCs [21,28]. Cimetidine also interrupt the effect of histamine on LPS-induced IL-10 and IL-12 production by monocytes [21]. Further, cimetidine abolish the preventive effects of a H2R agonist on the TNF-α by monocytes [29] (Fig. 1). When used as an

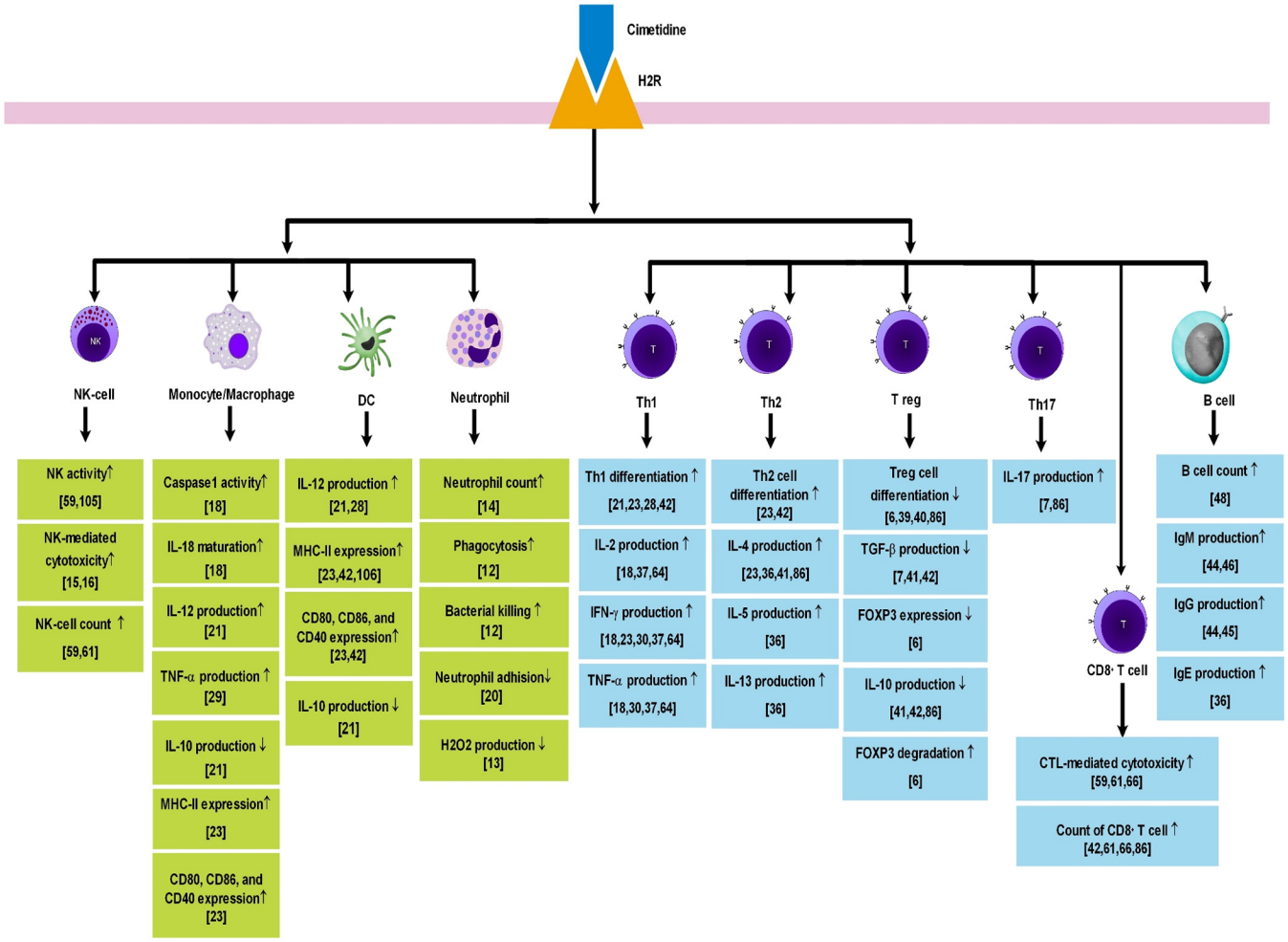

Fig. 1. Immunomodulatory effects of cimetidine. Cimetidine, as an H2R antagonist, reverses the histamine-mediated immunosuppression. Cimetidine has powerful stimulatory effects on the effector functions of innate- (including neutrophils, monocytes, macrophages, DCs, NK cells and NKT cells) [left side of Fig] and adaptive immunity (such as Th1-, Th2-, Th17-, regulatory T-, $CD8^+$ cytotoxic T cells, and B cells) [right side of Fig] through binding to histamine receptor 2 (H2R).

adjuvant, cimetidine increases the IL-12 and IFN-γ production, whereas reduces the IL-10 expression in mice vaccinated with a hepatitis B vaccine [30].

Cimetidine activates the PI3K-Akt signaling pathway and enhances the expression of the MHC-II and the costimulatory molecules (such as CD80, CD86, and CD40) in the murine macrophages and DCs [23]. Cimetidine also augments the HBsAg-induced up-regulation of IL-12 and TNF-α, while reduces the IL-10 in murine DCs. Therefore, cimetidine lead to the activation of the immunogenic DCs and inactivation of the tolerogenic DCs cells, which in turn potentiate antibody- and T cell-mediated responses through triggering of the both Th1- and Th2-cell polarization [23].

3.2. The effects of cimetidine on the T cells

One of the most efficient immunomodulatory effects of histamine is exerted on the T cell differentiation and function. Histamine suppresses the IL-2 production by mouse splenocytes through the induction of the protein kinase A [31]. Histamine also reduces the adhesion of $CD4^+$ T cells to extracellular matrix via H2R induction and the pre-treatment of T cells with H2R antagonists prevent this reducing effect [32].

The stimulation of the human $CD8^+$ T lymphocytes in the presence of the histamine lead to the higher IL-16 production, which is blocked by a histamine H2R antagonist [33]. However, histamine inhibits the activity of CTLs through binding to H2R [34]. The stimulation of the H2R on T-cells prevents the T lymphocyte-mediated graft versus host disease (GVHD). Cimetidine as an H2R antagonist cause GVHD relapsing due to the reducing of the function of suppressor T cells [8].

Both Th1 cell and Th2 cell-related responses are suppressed by H2R induction [8]. The H2R-deficient mice exhibit an up-regulation in the production of both Th1- and Th2 cell-related cytokines. Histamine up-regulates the IL-10 secretion from Th2 cells through acting on the H2R. The increased IL-10 expression by DCs and T cells may be a fundamental immunoregulatory mechanism by which histamine controls the inflammatory responses [8].

The induction of a powerful Th1 cell-mediated response is the most effective mechanism for the *Borrelia burgdorferi* elimination in the early stages of Lyme disease [30]. The cimetidine therapy promotes the levels of the Th1 cell-associated cytokines (such as IL-12, TNF-α and IFN-γ) while reducing the levels of the Th2 cell-associated cytokine IL-10 in patients with Lyme disease [30]. Cimetidine therapy during the early stages of *Borrelia burgdorferi* infection may improve the clinical outcomes of the Lyme disease [30].

It was also reported that the prevention of the histamine interaction with H2R using H2R antagonists such as ranitidine accelerate the proliferation of the Th2 cells and enhance the generation of the Th2 cell-linked cytokines representing the ability of H2R antagonists to potentiate the Th2 cell-mediated responses [35]. Moreover, intraperitoneal injection of cimetidine to mice enhances the antigen-specific IgE formation and Th2 cell-related cytokine expression [36]. On the other side, the potentiating impacts of cimetidine on the production of the Th1 cell-linked cytokines have been also demonstrated

[18,37]. Interestingly, it has been recently reported that cimetidine potentiate dual polarization of both Th1 and Th2 cells [23]. Collectively, these findings suggest that cimetidine reinforces both Th1 cell and Th2 cell-mediated immune responses (Fig. 1).

It has been proved that histamine suppresses the granulomatous reactions against *Schistosoma mansoni* in the infected mice and this suppression was related to the induction of H2R on suppressor T lymphocytes [38]. The histamine-mediated activation Treg cells lead to the suppression of the Th1 cell differentiation and augmentation of the Th2 cell differentiation [6]. Therefore, the blocking of the H2R on Treg cells promotes the Th1 cell-related pathways and thus reinforces the cellular immunity. The results from early studies were shown that cimetidine inhibits the effector function and the expansion of suppressor cells and Treg cells that express H2R [6,39,40].

The preventive impacts of cimetidine on Treg cells also alter cytokine profiles in vivo. Cimetidine down-regulates the expression such as IL-10 and TGF-β, which may lead to an impairment of $CD4^+CD25^+$ Treg cell-mediated suppression [41,42].

Cimetidine also reduces the FOXP3 (a key transcription factor in Treg cells) expression through modulating of the PI3K-Akt signaling pathway. Further, the cimetidine-mediated Stub1 expression lead to the ubiquitination and degradation of FOXP3 [6]. Cimetidine-mediated modulation of cAMP may also modulate the PI3K-Akt-mTOR pathway that leads to FOXP3 degradation with subsequent loss of Treg cell activity [6]. Therefore, in addition to the suppression of the FOXP3 expression, cimetidine also cause degradation of the FOXP3 protein with subsequent loss of Treg cell function [6].

Accordingly, cimetidine may directly or indirectly influence the Th1/Th2 cell-related immune responses. Cimetidine directly increases the frequency of both IL-4^+- (Th2) and IFN-γ^+ (Th1) cells in the $CD4^+$ T cell compartment [23]. Cimetidine also indirectly potentiates the Th1/Th2 cell-mediated responses through reducing the suppressive activity of the Treg cells [23].

It has been also shown that the transfer of H2R-deficient T cells into the SCID mice increases the severity of colitis and Th17 cell-related responses within the gut, in comparison with mice administrated wild type T cells [43].

Collectively, histamine exerts reducing effects on the Th1-, Th2- and Th17 cell-related immune responses, whereas having potentiating influences on the Treg cell-mediated immunosuppression via acting on H2R. Cimetidine as an H2R antagonist reverses the histamine effects on the effector T cells as reinforces the Th1-, Th2- and Th17 cell-related immune responses, while attenuates the Treg cell-mediated immunosuppression (Fig. 1).

3.3. The effects of cimetidine on the B cells

It has been shown that histamine directly suppresses the IgG and IgM production by in vitro-stimulated B cells [44]. Histamine via binding to H2R also reduces the antibody production after immunization in mice [45]. The mentioned suppression of the B cell-mediated antibody formation by histamine is prevented by treatment with cimetidine. The increasing effects of the cimetidine on the antibody production were indicated in other studies [44,46]. The subcutaneous administration of cimetidine (25 or 100 mg/kg/day) to tetanus toxoid-immunized mice lead to more production of the specific antibody (approximately twice) in response to vaccine [47]. Administration of cimetidine to SRBC-immunized mice also enhances the specific IgM response [46]. The stimulatory impacts of cimetidine on the antibody formation were higher in the secondary immune response compared with primary response. Further, low doses of cimetidine (such as 0.5–10 mg/kg) have more stimulatory influences on the IgM production in secondary response compared with higher concentrations (including 50–100 mg/kg) [46]. The number of B cells is also increased in cimetidine-treated patients with colorectal cancer [48]. Collectively, it seems that histamine exerts reducing effects on the antibody formation by B cells and cimetidine neutralize the histamine effects on the B cell-mediated antibody production (Fig. 1).

4. Therapeutic potentials of cimetidine as an immunomodulator

4.1. Immunomodulatory effects of cimetidine in malignant diseases

The immune system plays an essential role in the elimination of cancerous cells so that the patients with compromised immune responses are very susceptible to malignancy [49,50]. Some immune-related abnormalities were observed in cancer patients [51–55]. The elements of the innate immunity (such as NK cells, NKT cells, macrophages) and the elements of adaptive immunity (in particular specific CTLs and antibodies) exhibit antitumor activity [49,50]. However, the tumor cells escape from immune surveillance by several mechanisms, especially suppressing of the immune responses [50,51]. The aim of cancer immunotherapy is to potentiate the immune responses to eliminate the tumor cells [50].

The various types of effector CD4 + T cells perform different roles in the triggering of immune responses against malignant cells. Th1 cells express powerful anti-tumor activities through activating of the $CD8^+$ CTLs and NK cells as well as enhancing the expression of MHC and costimulatory molecules [50]. Conversely, Th2 cells prevent anti-tumor responses by suppressing of Th1 cells [54,56]. Treg cells are accumulated in the tumor tissues by chemokine CCL22 and express pro-tumor activity by suppressing of $CD8^+$ CTLs, Th1 cells, NK cells and APCs [55,56]. Th17 cells may display pro- or anti-tumor properties depending on the tumor type [56].

The accumulated mast cells in the tumor microenvironment and the malignant cells act as major producer of histamine during tumor development [57,58]. The elevated amounts of histamine were reported in some malignant patients, such as those with breast, prostate, ovarian, cervical and lung cancer. Although, histamine may induce certain tumor cell proliferation, however, its impact on the progression of tumors remains controversial [58]. The impacts of histamine on tumor development depend on histamine concentration, the tumor type and the subtype of HR. The expression of H2R were indicated in the lymphoma, leukemia, melanoma, breast-, colorectal-, cervical-, ovarian-, vaginal-, and vulvar cancer. Histamine cause tumor development as suppresses the anti-tumor immune response through induction of H2R [57].

The profitable impacts of cimetidine have been reported in several types of tumors in either humans or animal models such as colorectal cancer, gastric cancer, renal cell carcinoma, melanoma, glioblastoma, and lung cancer [57]. Cimetidine exerts anti-tumorigenic effects through suppression of the cancer cell proliferation, activation of macrophages, up-regulation of tumor suppressive cytokines, induction of apoptosis, reducing of tumor cell adhesion, decreasing of E-selection expression, inhibition of N-CAM expression, and suppression of angiogenesis through reducing the VEGF expression [59,60]. Moreover, the anti-tumorigenic effects of cimetidine may exert via the stimulation of appropriate immune responses, such as increasing the production of IL-2, IL-12, IL-15, IFN-γ, TNF-α and LT-β, increasing the number and activity of NK cells, improving the activity of tumor infiltrating lymphocytes (TIL), enhancing the immunostimulatory capacity of DCs, preventing the postoperative immunosuppression, preventing of postoperative alteration in the T cells and NK cells, and reducing the postoperative production of neutrophil elastase and IL-8 [59]. Cimetidine treatment also potentiate the TIL response at the tumor site that may reduce tumor aggressiveness [48,61].

As mentioned, in a mouse model of lung carcinoma, cimetidine reduces tumor growth and improves the survival of tumor-bearing mice [62]. Further, cimetidine reduces the accumulation of the CD11b + Gr-1 + myeloid derived-suppressive cell (MDSC) in the tumor tissue, spleen and blood of tumor-bearing mice. Cimetidine reverse the MDSC-mediated T cell suppression and improve the IFN-γ production [62].

Table 1
Summary of studies on immunomodulatory properties of cimetidine.

Models	Host[a]	Cimetidine doses	Treatment route	Treatment program	Results	Ref.
Neutrophils	Healthy subjects	0, 1, 10, and 100 mg/ml	In vitro	45 min[b] 5 min 10 min	- Production of O2− and H2O2.↓ - Increase in intracellular calcium concentrations.↓ - did not influence the neutrophils' chemotaxis or phagocytosis.	[13]
Hepato-cellular carcinomas	Wistar rats	100 mg/kg/day	Orally	7, 12, 22 and 32 weeks	- Hepatocarcinogenesis.↓ - Natural killer (NK) cell activity in splenic lymphocytes.↑ - proportion of NK cells among total splenic lymphocytes was not affected	[15]
Normal	Human	800 mg/day	Orally	3, 5, and 7 days	- Blood Leukocyte counts.↑ - Blood neutrophil counts.↑ - Blood number of CD3-positive T lymphocytes.↑ - Blood number of CD4-positive cells.↑ - Blood number of NK cells (not affected). - Blood number of NKT cells (not affected).	[14]
Monocytes	Healthy subjects	100 μM	In vitro	24 h	- IL-18 production.↑ - Activity of caspase-1.↑[c] - Intracellular cAMP levels.↑[d]	[18]
Human umbilical vein endothelial cells	Human	1 μM	In vitro	48 h	- Neutrophil adherence to HUVECs.↓ - Expression of the endothelial adhesion molecules E-selectin, P-selectin, and ICAM-1.↓	[60]
DCs and macrophages	C57BL/6 mice	5 μg/ml	In vitro	48 h	- The level of MHC II and CD40.↑ - CD80 was increased in the macrophage line. - Phosphorylation of PI3K, Akt, STAT-1, and NF-kB.↑	[23]
MDSCs and T cells co-culture	C57BL/6 mice	10^{-4} or 10^{-6} M	In vitro	72 h	- T cell proliferation.↑ - IFN-γ production by T cells.↑	[62]
MDSCs	C57BL/6 mice	10^{-4} or 10^{-6} M	In vitro	48 h	- MDSCs viability.↓ - MDSCs apoptosis.↑ - Caspase-3 levels.↑ - The Fas and FasL expression.↑ - NO production.↓ - Expression of Arginase I.↓	
Lung carcinoma	C57BL/6 mice	10 or 20 mg/kg/day	i.p	0, 2, 4, 6, 8, 10, 12 and 14 after the tumor inoculation	- Tumor growth.↓ - Survival rate of tumor-bearing mice.↑ - The number of splenic MDSCs in tumor-bearing mice.↓	
A cell line of lung cancer	Mice	10^{-8} to 10^{-4} M	In vitro	24 h	- No influence on tumor cell proliferation. - No influence on tumor cell apoptosis. - No influence on tumor cell migration.	
Gastro-intestinal cancer	Human	400 mg/day (before operation), 600 mg/day (after operation)	Orally	7 days before operation until 10 days after surgery.	- Blood number of total T cells.↑ - Blood number of helper T cells.↑ - Blood number of NK cells.↑ - Blood number of CD8 cells.↑ - Blood CD4/CD8 ratio.↑ - TIL response.↑	[61]
Colorectal cancer	Humans	800 or 1200 mg/day	Oral	10 days	- Blood number of $CD3^+$ and $CD4^+$ T cells.↑ - Blood number of $CD19^+$ B cells.↑ - TIL responses.↑	[48]
Viral warts	Humans	< 20 and 30 to 40 mg/kg/day	Oral	4 months	- 34.5% of the patients had a mark clinical improvement or complete remission of viral warts. - 23.6% of the patients had partial responses. - Expression of the IL-2 and IFN-γ in lesions.↑ - Expression of the IL-18 in lesions.↓ - Higher dose of cimetidine was more effective.	[37]
Burn injury	Balb/c mice	10 and 15 mg/kg/day	i.p	1–10 days post injury	DTH response	[68]
Burn injury	Balb/c mice	10 mg/kg/day	i.p	1–10 days post injury	- Delayed type hypersensitivity (DTH) response.↑ - Serum levels of IL-2, IL-10, IL-12 and IL-17.↑ - Serum levels of TGF-B.↓	[7]
Burn injury	Humans	15 mg/kg/day	Oral	4 days	- Cimetidine had no significant effect on the B cell count. - Cimetidine had no significant effect on the T cell count. - T cell proliferation.↑ - The number of $CD8^+$ T cells.↑	[66]
OVA-induced Allergic airway	Balb/c mice	50 mg/kg/day	i.p	Days 0, 2, 4, 6, 8, 10 and 12	- OVA-specific IgE.↑ - OVA-specific IgG1 and IgG2a.↑ - IL-5 and IL-13 production by spleen cells.↑ - IL-4, IL-5, IL-13 and IFN-γ levels did not change in the BALF.	[36]

(*continued on next page*)

Table 1 (*continued*)

Models	Host[a]	Cimetidine doses	Treatment route	Treatment program	Results	Ref.
Experimental Periodontitis	Holtzman rats	100 mg/kg/day	i.p	7, 15, 30, and 50 days after injury induction	- Alveolar bone resorption.↓ - RANKL/OPG cells.↓	[80]
Vaccination with HBV-DNA	C57BL/6 mice	100 μg of DNA vaccine premixed with 0.5% cimetidine	Intramuscularly	0, 14, and 28 days	- HBsAg-specific IgG.↑ - The ratio of IgG2a/IgG1.↑[e] - HBsAg specific DTH response.↑ - HBsAg specific T cell proliferation.↑[e] - HBsAg-specific $CD4^+$ T cell response (IFN-γ, IL-4, and IL-17A production).↑[e] - HBsAg-specific $CD8^+$ T cell response.↑[e] - Percentage of the splenic Treg cells.↓[e] - Production of IL-10 and TGF-β by splenic Treg cells.↓	[86]
Vaccination with HBV-DNA	C57BL/6 mice	100 μg of a DNA vaccine premixed with 0.5% cimetidine	Intramuscularly	0, 14, and 28 days	- The number of splenic HBsAg-specific $CD4^+$ $IL\text{-}2^+$ T cells.↑ The number of splenic HBsAg-specific $CD4^+$ IFN-γ^+ T cells.↑ - The number of splenic HBsAg-specific $CD4^+$ $IL\text{-}4^+$ T cells.↑ - The number of splenic HBsAg-specific $CD8^+$ IFN-γ^+ T cells.↑ - The number of splenic HBsAg-specific $CD4^+$ $CD25^+$ TGF-B^+ T cells.↓ The number of splenic HBsAg-specific $CD4^+$ $CD25^+$ $IL\text{-}10^+$ T cells.↓ - HBsAg-specific IgG and IgG2a.↑	[42]
Vaccination with HBV-DNA	C57BL/6 mice	100 μg of vaccine premixed with 0.25%–1.0% cimetidine	Intramuscularly	0, 14, and 28 days	- HBsAg-specific IgG1 and IgG2a.↑ - ratio of IgG2a/IgG1.↑ - HBsAg-specific T cell proliferation.↑ - HBsAg-specific DTH responses.↑ - The number of splenic HBsAg-specific $CD4^+$ IFN-γ^+ T cells.↑ - The number of splenic HBsAg-specific $CD4^+$ $IL\text{-}4^+$ T cells.↑ - The number of splenic HBsAg-specific $CD8^+$ IFN-γ^+ T cells.↑ - Regulatory function of CD4 + CD25 + Treg cells.↓ - The number of splenic $IL\text{-}12^+$ cells.↑ - The number of splenic $IL\text{-}10^+$ cells.↓	[41]
Vaccination with rHBsAg	C57BL/6 mice	rHBsAg premixed with 0.25%–1.0% cimetidine	Intramuscularly	0 and 14 days	- Production of IgG2a over IgG1.↑ - Proliferation of T cells.↑ - Frequency of $IL\text{-}4^+$ (Th2) and IFN-γ^+ (Th1) cells.↑ -Treg activity.↑ - The percent of the $CD11^+$ and $MHC\text{-}II^+$ cells in spleen.↑	[23]
Vaccination against Schistosoma japonicum	BALB/c mice	25 mg/kg/day	s.c	6 weeks	- Parasite egg number in the liver.↓ - Percentage of $CD4^+CD25^+Foxp3^+$ T cells in spleens.↓ - Serum levels of anti-parasite antibody.↑ - Splenocyte proliferation.↑ -IFN-γ and IL-12 production by splenocytes.↑ - IL-10 production by splenocytes.↓	[90]

[a] Host represents that the experiments were performed in vivo (in humans or in animals) or in vitro (on cells derived from human or animal sources).
[b] The 45 min, 5 min and 10 min was employed for measurement of chemotaxy, phagocytosis, and O2− and H2O2 production.
[c] This activity was measured at 1 h after cimetidine treatment.
[d] This activity was measured at 30 min after cimetidine treatment.
[e] This activities were observed when vaccine mixed with cimetidine and another adjuvant named praziquantel. The mice were immunized intramuscularly on days 1, 14 and 28 with 100 μg pEGFP-Sj26GST DNA.

Cimetidine also induce the caspase-associated apoptosis in MDSC by expressing Fas and FasL [62]. Therefore, cimetidine may improve anti-tumor immune responses through inhibiting of the MDSC and induction of apoptosis in these cells (Table 1).

The Treg cell-mediated immunosuppression also plays a critical role in cancer development [51,52,56]. As mentioned cimetidine has profound preventive effects on the Treg cell activity [6,41,42]. Therefore, the beneficial influences of cimetidine on cancer outcome may perform in part through inhibition of Treg cell functions and subsequent stimulation of anti-tumor immunity.

The results from an investigation in patients with gastrointestinal cancers showed that the count of the total T cells, Th cells and NK cells was progressively reduced with the tumor advancement [61]. The treatment with cimetidine improves percentages of total T cells, Th cells and NK cells than the control individuals [59,61]. Cimetidine may also directly suppress tumor cell expansion [61].

4.2. Immunomodulatory effects of cimetidine in warts

Human papilloma virus (HPV) causes cutaneous warts, which commonly affect children and adolescents [63,64]. In immunocompetent individuals, warts frequently regress in spontaneous

manner. However, in patients with compromised cell-mediated immunity (such as AIDS or organ transplantation), the warts are recalcitrant and persist as a result of immunosuppression [63]. Administration of the cimetidine (at doses 30–40 mg/kg/day for 3 to 6 month duration) to eight pediatric recipients of heart transplant with multiple recalcitrant warts lead to the complete improvement of the lesions except in one patient [64]. The results from several trials also indicate that cimetidine at doses ranging from 25 to 40 mg/kg/day (or from 400 to 800 mg three times per day) has beneficial effects on the wart regression [65]. Oral administration of the cimetidine in various doses (ranging from < 20 to 40 mg/kg/day for up to 4 months) in patients with several viral warts results in the dramatic clinical improvement or full remission of lesions in the majority of patients. The expression of the IL-2 and IFN-γ is increased while the expression of the IL-18 was reduced in the lesions from cimetidine-treated patients [37] (Table 1). Higher dose of oral cimetidine were more efficient in improving of the viral warts. Cimetidine may be more effective at high doses to inhibit the suppressor T cell activity [64].

Cimetidine activates Th1 cells to produce IL-2, TNF-α, and IFN-γ and their expression correlates with improvement in cellular immunity and wart remission [37,64]. The stimulatory effects of the cimetidine on $CD8^+$ CTLs may perform a key role in the elimination of the in viral infection [66]. These mentioned findings indicated that cimetidine effectively improves viral warts due to its stimulatory effects on the immune system.

4.3. Immunomodulatory effects of cimetidine in burn

Infection remains the major cause of mortality and morbidity in burn-injured patients. Thermal injury induces immunosuppression that makes burn patients vulnerable to infectious agents [67]. The effector mechanisms of innate- (such as phagocytosis) and adaptive (including T cell responses and antibody production) immunity, are adversely affected by thermal trauma [67,68]. It should be noted that the plasma and tissue levels of histamine are elevated during a post-burn period that may play a critical role in the post burn-related immunosuppression [69]. Thus, the cimetidine capacity for the restoration of immune competence in post-burn period may in part due to the reversing of the histamine immunomodulating effects.

In a mouse model, it has been shown that cimetidine restore the burn-induced suppression of DTH response after thermal injury [68] (Table 1). Cimetidine also abrogates the burn blister fluid- and sulfur mustard-induced immunosuppression [70,71]. Experimentally, it was also shown that cimetidine (at a dose of 10 mg/kg) also increases the serum concentrations of IL-2, IL-10, IL-12, and IL-17 following thermal burn injury [7]. However, the serum levels of TGF-β were reduced in cimetidine-treated burn mice [7] (Table 1).

Moreover, the administration of the cimetidine at a dose 15 mg/kg/day (for 4 days) to burn-injured patients improve the T-cell proliferation and enhance the percentage of $CD8^+$ T cells [66]. However, the percentage of the $CD3^+$ and $CD4^+$ T cells and the percentage of the B cells ($CD19^+$ $HLA\text{-}DR^+$ cells) were not changed in cimetidine-treated patients compared to control untreated thermally-injured individuals [66] (Table 1). Cimetidine has also beneficial effects in countering burn wound itch [72]. The mentioned information may be utilizable for clinicians to prevent the burn-induced immunosuppression and reduce the risk of infections using cimetidine.

4.4. Immunomodulatory effects of cimetidine in allergic diseases

The stimulation H2R of histamine placed on T lymphocytes diminish inflammatory responses and promote the suppressive activities that reduce the inflammation [8]. Therefore, the induction of H2R on the T lymphocytes may prevent the inflammatory responses. Histamine reinforces the inhibitory effects of TGF-β on T lymphocytes via binding to H2R and the Th2 cell are more susceptible to histamine-enhanced TGF-β suppression [73]. Histamine has also suppressive effects on the IFN-γ secretion by Th1-like cells separated from peripheral blood sample or from bronchial biopsy in atopic patients, but has no significant influence on the IL-4 production by Th2-like cells [9]. Histamine also reduces the IL-4 and IFN-γ production by Th0 clones [9].

In atopic patients, the number of T lymphocytes expressing H2R is lower compared with healthy individuals [74]. The peripheral lymphocytes and PBMCs from atopic patients produce lower histamine-induced immunosuppression activity in comparison with non-atopic, healthy individuals [74]. In asthmatic patients, a positive association was reported between the abnormality in the suppressor cell activity and low expression of H2R on the lymphocytes [8].

Administration of cimetidine to mice sensitized with OVA promotes the production of the Th2 cell-related cytokine by OVA-stimulated spleen cells and enhance the serum amounts of specific Th2 cell-dependent IgE and IgG1 and IgG2a [36]. Cimetidine also promotes the formation of the Th1 cell-dependent specific IgG2a. Therefore, cimetidine potentiates both Th2 cell- and Th1 cell-related responses [36]. It seems that the enhanced Th2 cell responses may be suppressed by the cimetidine-mediated increasing in Th1 responses that lead to the limitation of the local inflammatory reactions [36] (Table 1). In addition, the cimetidine administration reduces the numbers of $CD4^+$ T cells, increases the numbers of $CD8^+$ T cells and reduces the IgE levels in the nasal secretion of the patients with allergic rhinitis [75]. Therefore, H2R may be a suitable target to regulate the allergen-specific T lymphocytes in allergic responses.

4.5. Immunomodulatory effects of cimetidine in bone resorption

The osteoclasts and the RANK and RANKL molecules are among of the most players in the bone resorption in disorders such as arthritis and periodontitis [76,77]. RANKL is expressed by many lymphoid and non-lymphoid cells. The binding of RANKL to RANK on the cell membrane of osteoclast progenitors promote their differentiation [76]. The induction of the RANK on the cell membrane of osteoclasts also leads to their activation that perform an essential role in the bone resorption [77]. However, OPG (that is expressed by various cells, including osteoblasts, endothelial cells, gingival fibroblasts, and epithelial cells) inhibits osteoclastogenesis through the prevention of the RANKL binding to RANK, therefore acts as a protective factor against bone loss [76,77]. In periodontal diseases, high expression of the RANKL and occurrence of a diversion in the RANKL/OPG balance was associated with bone resorption [76]. It has been found that the addition of the histamine to a culture of bone marrow cells induces the RANKL secretion, suggesting that this mediator may stimulate osteoclast formation [78]. Moreover, histamine receptor antagonists decrease the inflammatory response and bone loss in experimentally induced arthritis and periodontal disease in rabbits, suggesting that this mediator may interfere with bone metabolism [78]. Cimetidine inhibits the bone resorption through reducing the number of osteoclasts [79]. Recently, a significant reduction was also indicated in the number of $RANKL^+$ cells in the periodontal ligament in cimetidine-treated rats [79]. In an experimental model of periodontitis, the treatment with cimetidine also decreases the alveolar bone resorption and reduces the ratio of RANKL/OPG positive cells [80] (Table 1).

4.6. Immunomodulatory effects of cimetidine in vaccination

Approximately, 290 million persons have been chronically infected with hepatitis B virus (HBV), worldwide [81]. The HBV specific Th1- and CTL-mediated responses contribute to HBV elimination confirm an efficient protection against infection [81]. The universal vaccination of neonates and children with HB vaccine was also considered as an effective strategy to control HBV infection [82]. Vaccination with HBsAg induces a protective antibody response (anti-HBs ≥ 10 IU/L) in the high percentages (90–99%) of vaccines [83,84]. However, the

protective amounts of anti-HBs antibody are not produced in a low proportion of vaccines [85].

The production of the anti-HBs antibody is regulated by a coordination between specific Th1- and Th2 cells and the lack of an antibody response to HBsAg was attributed to insufficient production of both Th1- and Th2 cell-related cytokines [83]. The genetic parameters, in particular HLA molecules, imperfection in antigen presentation, defect in HBsAg-specific T and B cell repertoire, and increasing in the Treg cell activity may also contribute in unresponsiveness to HB vaccine [82].

Using murine models, it has been demonstrated that the mixing of HB DNA vaccine with cimetidine increases the HBsAg-specific IgG, enhances the specific IgG2a/IgG1 ratio, promotes the HBsAg specific DTH response, augments the HBsAg specific T cell proliferation, increases the HBsAg-specific $CD4^+$ T cell response (IFN-γ, IL-4, and IL-17A production), enhances the HBsAg-specific $CD8^+$ T cell response, increases the number of splenic HBsAg-specific $CD4^+$ $IL\text{-}2^+$ T cells, augments the number of splenic HBsAg-specific $CD4^+$ IFN-γ^+ T cells, augments the number of splenic HBsAg-specific $CD4^+$ $IL\text{-}4^+$ T cells, and enhances the number of splenic HBsAg-specific $CD8^+$ IFN-γ^+ T cells [23,41,42,86]. However, the combination of the DNA vaccine with cimetidine reduces the number of splenic HBsAg-specific $CD4^+$ $CD25^+$ TGF-β^+ Treg cells, decreases the number of splenic IL-10^+ cells, diminishes the number of splenic HBsAg-specific $CD4^+$ $CD25^+$ IL-10^+ T cells, and reduces the IL-10 and TGF-β production by splenic Treg cells [23,41,42,86]. In addition, cimetidine enhances the expression of costimulatory markers (such as CD86, and CD80) as well as MHC-II in DCs [42]. The PI3K-Akt signaling pathway is also activated in DCs by cimetidine [42] (Table 1).

These findings suggest that cimetidine potentiate the immune responses of HBV DNA vaccine through the stimulation of the specific Th1 cell-, Th2 cell- and Th17 cell-related responses and inhibition of the Treg cell-associated cytokine expression patterns [41]. Therefore, cimetidine reinforces both antibody- and T cell-mediated immune responses to HB DNA vaccine. Further, cimetidine has more advantages in comparison with the FDA-approved adjuvant alum, as it has the capability to suppress the IL-10 production and potentiate the Th1/Th2 cell dual polarization [23]. Accordingly, cimetidine may be consider as an efficient therapeutic adjuvant, where dual polarization of Th1- and Th2 cells should be induced to effectively eliminate a viral infection.

Another health problem is the schistosomiasis, as about 240 million individuals suffer from this infection, worldwide [87]. The Th1 cell-derived cytokines, in particular IFN-γ, provide an efficient immunity against schistosome through activating of macrophages and endothelial cells [88]. However, the schistosome-induced Treg cells play a key role in the suppression of the protective immune response and help the parasite to escape from the immune system [88,89]. The results from an experimental study are showing that the administration of the cimetidine during vaccination against Schistosoma japonicum reduces that number parasite egg in the liver after challenge with parasite, reduces the number of Treg cells in splenocytes, reduces the IL-10 production by splenocytes, increases the IFN-γ and IL-12 production by splenocytes, enhances the splenocyte proliferation, and increases the serum levels of anti-parasite antibody [90] (Table 1). However, the results from an investigation in healthy volunteer individuals are showing that the oral administration of the cimetidine has no considerable effects on the formation of the specific antibodies after vaccination with a group B meningococcal vaccine [91].

Immunization of the BALB/c mice with the ROP2 protein of *Toxoplasma gondii* mixed with cimetidine lead to the higher induction of serum specific IgG, higher ratio of $CD4^+/CD8^+$ T cells in spleen, higher proliferation of splenocytes, higher serum levels of IFN-γ and longer survival time after challenge with parasite in comparison to mice immunized with protein alone [92].

Cimetidine may enhance immune response to a vaccine in different ways, such as blocking the histamine-mediated immunosuppression, increasing of the DC functions, potentiation of the Th1 and/or Th2 cells, and decreasing of the Treg cell activity.

5. Immunomodulatory effects of other H2R antagonists

H2R antagonists are structurally analogues of histamine and the most popular H2 blockers include cimetidine, ranitidine, famotidine and nizatidine. Ranitidine is a modified cimetidine, as it lacks an imidazole ring, but contains a furan ring [20]. Famotidine and nizatidine are structured based on a thiazole ring [20,93]. Other than cimetidine, there are rare reports concerning the immunomodulatory effects of other H2R antagonists.

In murine models of breast cancer, it was indicated that ranitidine enhances the antitumor antibody response, reduces the MDSC population and inhibit tumor growth [94,95]. Ranitidine also enhances the IL-2 production by mitogen-activated murine spleen cells [96]. Moreover, the NK cell activity and the PHA-induced T-cell proliferation were improved in ranitidine-treated HIV patients [97]. The anti-polysaccharide antibodies in B-CLL patients vaccinated with a conjugated vaccine against Haemophilus influenzae type-B were also higher in ranitidine-treated group compared with untreated patients [98]. Further, treatment of allergic rhinitis patients with ranitidine enhances the serum amounts of IFN-γ and reduces IL-4 and IgE levels [99]. The combination of IL-2 and ranitidine also improves the in vitro NK cell activity of patients with colorectal cancer [100]. In addition, ranitidine reverses the surgery-induced immune suppression, increases the mitogen-stimulated IFN-g production and enhances the number of $CD4^+$ T cells in patients with head injury [101].

The investigations regarding the immunomodulatory effects of famotidine and nizatidine are more limited. It has been indicated that histamine suppresses the TLR-mediated TNF-α and IFN-γ secretion from human PBMCs and famotidine completely abolish the histamine-mediated inhibitory effects on cytokine production [43]. Moreover, famotidine disrupts the inhibitory effects of histamine on the LPS-induced TNF-α production and B7-1 expression by monocytes [102]. Further, histamine inhibits the production of Th1 cell- related cytokines (IFN-γ, TNF-α and IL-2) and IL-4 in murine intestinal intraepithelial lymphocytes. The famotidine interrupt the mentioned inhibitory effect of histamine on cytokine production [103].

The immunization of mice with an avian influenza vaccine (H5N1 killed viral antigen) plus nizatidine also enhances the specific Th1- and Th2 cell-mediated responses, upregulates the MHC-II, CD40 and CD86 expression on APCs, upregulates the IL-12 and TNF-α production by spleen cells, downregulates the IL-10 production by spleen cells, enhances the frequency of both IFN-γ and IL-4 producing cells and reduces the frequency of Treg cells in spleen as compared with control mice immunized with H5N1 antigen alone [104]. After a lethal H5N1 viral challenge, the survival rate was higher in mice immunized with antigen plus nizatidine compared with the control group [104].

The immunomodulatory effects of H2R antagonists were also compared in a few of comparative studies with conflicting results. In one comparative study, it was observed that only cimetidine (and neither ranitidine nor famotidine) increase the NK cell activity, inhibit suppressor T cell activity, promote IL-2 production, and increase proliferative response of lymphocyte to mitogen in PBMCs from patients with gastric cancer [16]. In another study, the effects of cimetidine and famotidine were evaluated on the NK activity in patients with hepatocellular carcinoma and cirrhosis. Only cimetidine improved the NK cell activity [105]. Further, cimetidine (and no famotidine) enhanced the antigen presenting capability of DCs from colorectal cancer patients [106]. In addition, only cimetidine (and neither ranitidine nor famotidine) has been reported that inhibit the glucose-induced expression of adhesion molecules ICAM-1 and P-selectin on endothelial cell reduce the neutrophil–endothelial cell adhesion [20]. Profound differences were also reported regarding the antioxidant properties, anti-proliferating effects and apoptosis induction in tumor cells of cimetidine,

ranitidine, and famotidine [107–109]. These studies clearly indicate that there are considerable differences between H2R antagonists regarding their immunomodulatory properties. These differences may be due to structural variations among H2R antagonists. Unlike cimetidine, ranitidine and famotidine lack the imidazole ring. The structural differences between H2R antagonists may influence their binding affinity to receptors and may affect the H2R-related signaling pathways. Cimetidine seems to be a superior element for immunomodulation and aforementioned its immunomodulatory effects were attributed to H2R antagonist activity. As mentioned, there are sharp differences between H2R antagonists regarding their immunomodulatory effects. Although not yet verified, however, all of the immunomodulatory effects cimetidine may be not exerted solely through the H2 receptor. In other words, the immunomodulatory effects of cimetidine may be exerted through both H2R-dependent and H2R-independent pathways.

6. Conclusion

In this review, we have explained that histamine exerts profound effects on the various types of leukocytes through binding to H2R. Of note, cimetidine, as an H2R antagonist, interfere with all of the major histamine effects on the leukocytes. The results from experimental and some clinical studies indicate that cimetidine has the potentials to improve the immunological parameters in cancers, viral warts, allergies, burn, bone resorption, and vaccination. A better understanding regarding the immunomodulatory potentials of cimetidine for the possible managing of immune-related disorders was provided in this review. However, the standardization of the treatment with cimetidine regarding its effective immunomodulatory doses, administration routes and the duration of treatment in preclinical therapeutic program needs more consideration.

Conflict of interest

The authors have no any conflict of interest.

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