

Assessment of Agomelatine Possible Protective Effect in Ulcerative Colitis Patients; An Overview

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Abstract

Background: *Ulcerative colitis, a life-long recurrent relapsing-remitting disorder, is a type of debilitating chronic IBD of the colon that causes a superficial mucosal inflammation in a continuous fashion extending from the rectum to the more proximal colon, in varying extents. The hallmark symptoms of UC include bloody diarrhea with rectal urgency and tenesmus. Many UC patients experience extra intestinal manifestations (EIM) that involve multiple organs like erythema nodosum, pyoderma gangrenosum and arthritis. mucosa of the GIT is exposed to millions of antigens from the food, environment and microbiome. The epithelial barrier, covered by a mucinous layer, is the first-line defense of the mucosal immune system, because it provides physical separation between host immune cells and luminal microbes.*

Treatment of UC consists mainly of 5-aminosalicylates (5-ASAs), corticosteroids, immunosuppressive drugs, and monoclonal antibodies to TNF- α . Treatment success is dependent on several factors, such as use of the right drug for the right indication (induction vs maintenance), optimization of the dose, and maximization of drug adherence (non-adherence to mesalazine is associated with increased rates of relapse). Treatment should be tailored to disease activity (mild, moderate, severe) and the extent of colonic involvement (proctitis, left-sided colitis, or pancolitis).

Agomelatine is an atypical antidepressant with a unique receptor profile, as a melatonin receptor (MT1 and MT2) agonist and a 5-HT_{2C} receptor antagonist.

Keywords: *Agomelatine, Ulcerative Colitis (UC), Mesalazine.*

1. Introduction:

Ulcerative colitis, a life-long recurrent relapsing-remitting disorder, is a type of debilitating chronic IBD of the colon that causes a superficial mucosal inflammation in a continuous fashion extending from the rectum to the more proximal colon, in varying extents(1).The hallmark symptoms of UC include bloody diarrhea with rectal urgency and tenesmus. Many UC patients experience extra intestinal manifestations (EIM) that involve multiple organs like erythema nodosum, pyoderma gangrenosum and arthritis (2).

2. Epidemiology and risk factors

Wilks. (49) was the first who described UC in 1859 and reported that UC is more common than Crohn's disease (CD). Ulcerative colitis is more common in the industrialized world, particularly North America and Western Europe. Worldwide, the incidence of UC is on the rise with the annual incidence of UC ranging from 8.8 to 23.1 per 100,000 person/year in North America, 0.6 to 24.3 per 100,000 person/year in Europe (3).

At the turn of the twenty-first century, the incidence of UC has stabilized in developed nations, however, it has actually risen in many newly industrialized countries within South America, Asia, Africa and the Middle East. Although prevalence remains low in these countries, it is expected to climb given the rising number of new UC diagnoses (3,4), the emergence of IBD in these areas strongly implicates the role of environmental risk factors to the development of the disease (5).

The risk factors for UC can be classified as follow:

➤ A) Non-modifiable factors:

(1) Age and gender: Ulcerative colitis has a bimodal age distribution with incidence peak in the second to fourth decade of life followed by a second smaller peak occurring in the sixth to seventh decades of life with up to 10% to 15% of new diagnoses occurring after the age of 60 years (6).

No consistently significant difference has been observed between rates of UC among men and women, however some studies demonstrate a male predominance in UC (7).

(2) Race and ethnicity: Jewish population has a 3-fold higher risk of IBD than non-Jewish populations (1).Initial studies reported a markedly lower prevalence of IBD among African-American and Hispanic ethnicities when compared to the white populations, however recent studies suggest that the gap in incidence between white and non-white populations is narrower than first thought, with comparable phenotypes (8).

(3) Genetics: About 8–14% of patients with UC have a family history of IBD, more commonly UC. The relative risk of developing UC for first-degree relatives of a patient with UC is estimated to be 4.5% in Jewish probands when compared with 1.6% in non-Jewish probands. Twin studies have shown that the concordance rates in monozygotic twins are estimated at 16% for monozygotic and 4% for dizygotic twins (9).

Several studies have attempted to identify genetic predictors of severe clinical course of UC. Based on genome-wide association study (GWAS), Tumor necrosis factor superfamily member-15 (TNFSF-15) locus has been reported to increase the risk of severe UC. Other studies have identified polymorphisms in the IL-1 β gene as a predictor for severe UC (10).

➤ B) Modifiable factors:

(1) Environmental factors: Incidence of ulcerative colitis is higher in developed countries than in developing countries, and in urban versus rural areas (11). It is believed that genetically predisposed patients, when in contact with environmental factors, develop an inadequate immune

response that ultimately causes inflammation of the gastrointestinal tract (GIT) (12).

The increased incidence in developed countries could be partly explained by increased access to health care and better medical records in more developed than less developed countries. Furthermore, improved sanitation in industrialized countries might reduce exposure to enteric infections during childhood, thus restricting maturation of the mucosal immune system, which could result in an inappropriate immune response when exposure to infectious microorganisms occurs later in life (13).

(2) Diet: Development of IBD has been postulated to be an immunologic response to food antigens. The association of a "Western" style diet (processed meat, refined carbohydrates, etc.) is associated with an increased risk of developing IBD (14)

Cow's milk protein hypersensitivity during infancy has been postulated as a possible cause of UC (1). Increased dietary intake of total fat, animal fat and poly unsaturated fatty acids are also correlated with an increased incidence of UC (15).

Breast milk is frequently one of the earliest diets provided to infants. Breast feeding is protective against subsequent development of ulcerative colitis, but only when the duration of breast feeding is more than 3 months (16), studies have found that breast feeding may have an impact on the subsequent development of immune-mediated diseases by maintaining the integrity of the epithelial barrier, preventing infections, and also providing direct immunologic benefits (17).

(3) Microbiota: Several epidemiological clues point toward dysbiosis of the intestinal microbiota in IBD. Dysbiosis is defined as an altered composition of the commensal bacterial populations, leading to the dysregulation of the immune response to bacterial antigens (18).

Patients with UC have disturbances in the composition of their gut microbiota, with lower proportions of Firmicutes (phylum) and Bacteroides (genus) and higher proportions of Enterobacteriaceae family, studies have also found decreased loads of Clostridia in UC. These bacteria produce short chain fatty acids (SCFAs), such as butyrate, which serve as an energy source for colonic cells and also possess anti-inflammatory properties. It has therefore been postulated that decreased SCFAs can result in increased inflammatory responses and epithelial nutrient deficiency (19).

The fact that antibiotic therapy has no clinical effect on UC argues against an important role of bacteria in UC, whereas antibiotics do provide some benefit in luminal CD. Serum antibacterial antibodies are present in patients with UC like perinuclear antineutrophil cytoplasmic antibody (p-ANCA), but they are much more common and found in higher titers in patients with CD(7).

Also, abnormality in enteric virome has been reported in UC with expansion of bacteriophages belonging to the Caudovirales family independent of bacterial dysbiosis (20).

(4) Appendectomy: Appendectomy has a divergent effect on UC and CD. Based on a large cohort study, the risk of developing UC was decreased by about 55% in those who underwent appendectomy before they were 20 years old for an inflammatory condition (appendicitis or mesenteric lymphadenitis), but not for non specific abdominal pain. In contrast, the risk of CD was increased after appendectomy (21).

In patients with UC, a prior appendectomy was associated with clinically milder disease, lower relapse rates, reduced need for immunosuppression, but had no clear effect on risk of colectomy(22).

3. Agomelatine

Agomelatine is an atypical antidepressant with a unique receptor profile, as a melatonin receptor (MT1 and MT2) agonist and a 5-HT_{2C} receptor antagonist (23).

3.1. Discovery strategy and development

It was firstly introduced in the market in 2009 after receiving official approval from the European Medicines Agency (EMA). It is licensed for Major Depressive Disorder (MDD) treatment in adults and is available as a 25 mg tablet with the range of daily dosage recommended between 25 and 50 mg. Since its introduction to the market, agomelatine's efficacy and safety are broadly proven and recent network meta-analysis of 21 antidepressant drugs for the acute treatment of depression puts agomelatine in the frontline of 'the top three' antidepressants in terms of both efficacy and tolerability for MDD treatment (24). Moreover, in terms of cost-effectiveness data indicates that agomelatine might be of value for money option (25).

The discovery and development of agomelatine were based on two basic principles:

- (a) designing the first antidepressant that would target the disturbed circadian rhythms in depression
- (b) introducing an antidepressant with a mechanism of action extending beyond monoaminergic neurotransmission (26).

3.2. Chemistry:

Agomelatine is N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide, is a naphthalene bio isostere and a synthetic analogue of melatonin (Figure I). In mammals; melatonin, an endogenous hormone, is secreted by the pineal gland, primarily at night. It participates in the regulation of circadian rhythms and it is involved in the seasonal reproduction patterns (27).

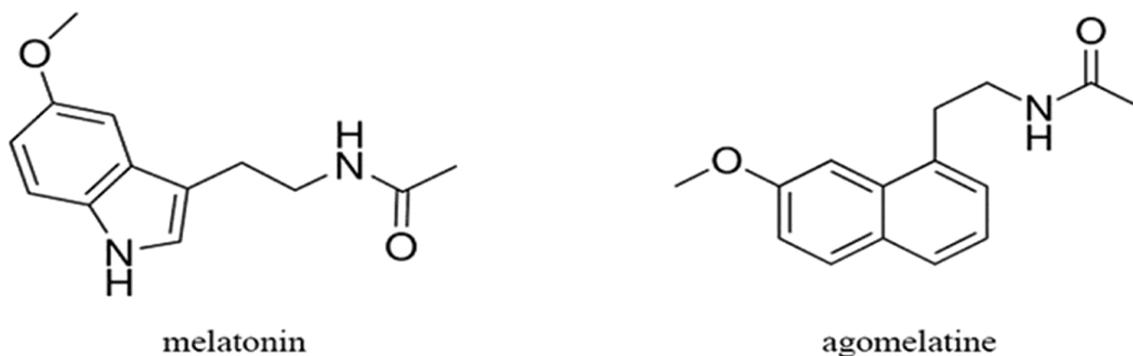


Figure (I) Chemical structure of melatonin and agomelatine (28).

3.3. Pharmacokinetics of agomelatine

Agomelatine is rapidly (0.5–4 hours) and well absorbed after oral administration (29). However, its bioavailability is 5% at the therapeutic oral dose, increased in females and displays significant variation between individuals due to the high first-pass metabolism which may be of concern especially in elderly patients or in subjects with liver disorders (30).

It presents a moderate volume of distribution of approximately 35 L and a short plasma half-life (1–2 h). A plasma protein binding of 95%, Albumin and alpha L-acid glycoprotein are the main plasma binding proteins (30).

At the therapeutic levels, agomelatine blood concentration increases proportionally with dose; at higher doses, a saturation of the first-pass effect may occur. About 80% of the drug is eliminated through urinary excretion of the metabolites, whereas a small amount of the metabolites undergoes

fecal excretion (27). The major enzymes involved in the biotransformation of agomelatine are cytochrome CYP1A2 (90%), and to a lesser extent, CYP2C9/CYP2C19 (31).

3.4. Pharmacodynamics of agomelatine:

Agomelatine acts as agonist of melatonergic MT1 and MT2 receptors with a longer half-life and higher affinity for these receptors than melatonin and acts as antagonist with moderate affinity for serotonergic 5-HT_{2C} receptors and no significant affinity for other neuroreceptors (32).

Melatonergic receptors are not only expressed in the central nervous system, in particular in suprachiasmatic nucleus, hippocampus, striatum, nucleus accumbens, caudate, putamen, retina, but they are also distributed in peripheral systems such as the GIT (29).

In the gastrointestinal system, melatonin receptors are found most commonly in jejunal and colonic mucosa, Melatonin has been shown to be a potent reactive oxygen metabolite scavenger and antioxidant that affects many physiological functions including secretion, motility, digestion and absorption of the GIT. In addition, melatonin has anti-inflammatory effect that may contribute to the protection of the gastrointestinal mucosa (33).

As a member of the superfamily of G protein-coupled receptors, MT1 and MT2 are capable of influencing a number of signaling cascades through the heterotrimeric guanine nucleotide binding proteins, they are coupled mainly to (G_i) proteins (Figure II). Activation of melatonin receptors leads to the dissociation of the heterotrimeric G proteins, the G_α subunit and G_{βγ} complex, thereby interact with various downstream effectors. Upon receptor activation, melatonin receptors primarily inhibit adenylyl cyclase (AC) via the pertussis toxin (PTX)-sensitive G_i proteins (G_{αi2} and G_{αi3} isoforms) (34). The decline in cyclic Adenosine Mono Phosphate (cAMP) subsequently suppresses protein kinase A (PKA) activity and nuclear factor CREB (cAMP responsive element binding protein) phosphorylation. Melatonin has been shown to play a role in the rhythmic regulation of clock gene expression via the Adenyl Cyclase/cAMP pathway (35).

The major difference between MT1 and MT2 receptors at the signaling level is the ability of MT2 receptor to inhibit cyclic Guanosine Mono Phosphate (cGMP) production beside their inhibition of cAMP (36).

Agomelatine is also a serotonin “5-hydroxy tryptamine” (5-HT_{2C}) receptor antagonist. 5-HT_{2C} is coupled via G_{αq/11} to activate phospholipase C (PLC), which generates Diacylglycerol (DAG) and inositol-1,4,5-triphosphate (InsP₃) from membrane localized phosphoinositide. InsP₃ stimulates the release of calcium from the endoplasmic reticulum (ER), which, together with DAG, activates protein kinase C (PKC), leading to the phosphorylation of various cellular substrates (37).

3.5. Agomelatine as antidepressant

The synergistic effect of melatonergic agonism and serotonin antagonism rather than isolated actions of both mechanisms, may explain both the anxiolytic and anti-depressive effects of agomelatine (31).

Cellular effects elicited by agomelatine include activation of cell proliferation, maturation and survival in the ventral hippocampus, increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex, increased expression of activity-regulated cytoskeleton associated protein (Arc) in the frontal cortex, and increased glutamate release in the prefrontal and frontal cortices (38).

In addition, agomelatine may modulate gamma amino butyric acid (GABA) pathway by the activation of GABA-neuron and this anxiolytic activity may be potentiated by its receptor antagonism on 5-HT_{2C} receptor (29).

Agomelatine has also been documented to resynchronize circadian rhythms, more ever, MT₁ and MT₂ receptors are involved in the regulation of sleep and the expression of MT₁ is upregulated by night, so agomelatine is considered as a good sleep inducer (39).

Agomelatine indirectly increases dopamine and norepinephrine release in the frontal cortex. It has no effect on extracellular serotonin levels, as opposed to other antidepressants. The stimulant effects of agomelatine on these monoaminergic systems contribute not only to its antidepressant action, but also to improved neurocognitive functions, especially memory, attention and problem solving (40).

Specific components of the immune/inflammatory system play a crucial role in the antidepressant response and thereby in depression etiopathology. Chronic treatment with agomelatine significantly reduced the lipopolysaccharides (LPS)-induced up-regulation of the pro-inflammatory cytokines IL-1 β and IL-6 in the rat brain as well as at peripheral level, and also decrease TNF- α levels in major depressive patients (41).

Agomelatine also altered the expression of enzymes related to the kynurenine pathway which represent important mediators in inflammation-related depression. Thus, agomelatine appears to interfere with molecular systems involved with inflammatory responses (42).

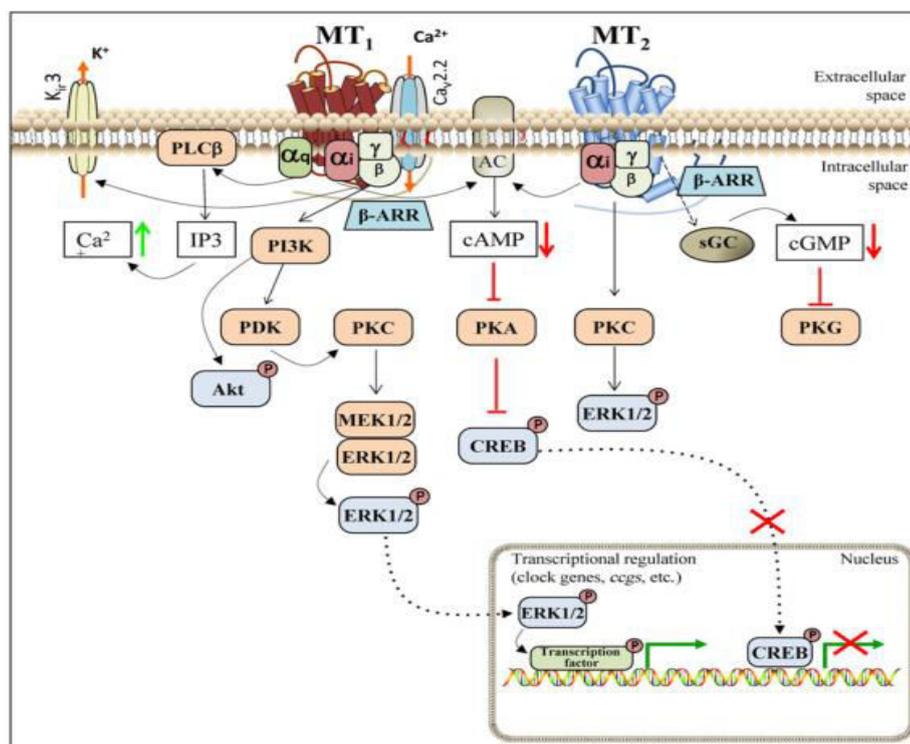


Figure (II): Melatonin receptor signaling pathways. Melatonin activation of MT₁ receptors triggers G α_i activation, decreasing the levels of the secondary messenger cAMP, and G β dependent activation of PI3K/Akt, PKC and ERK pathways. MT₁ coupling to G α_q leads to PLC

activation and increase in intracellular Ca²⁺. Melatonin-induced modulation of neuronal action potential is mediated by MT1-dependent activation of the potassium and calcium ion channels (Kir3 and Cav2.2). The physical interaction of MT1 receptors with Cav2.2 channels tonically inhibits Cav2.2-mediated calcium entry through Gβγ subunits. Melatonin activation of MT2 receptors triggers Gαi-dependent cAMP and ERK signaling pathways and inhibits cGMP levels. Melatonin induced β-arrestin recruitment to both MT1 and MT2 receptors, but β-arrestin-dependent down-streaming signaling is not yet reported. PI3K/Akt, phosphoinositide 3-kinase/serine/threonine kinase-1; ERK, extracellular-regulated kinase; β-ARR, β-arrestin; Cav2.2, voltage-gated calcium channel; cccgs, clock-controlled genes; CREB, cAMP-responsive element binding; Kir3, G protein-coupled inwardly rectifying potassium channel; sGC, soluble GC (36).

3.6. Clinical uses:

Antidepressant for Major Depressive Disorder (MDD)

Agomelatine proved to be effective in the treatment of the acute phase of depression (40). Agomelatine is the first reported melatonergic drug having anxiolytic and antidepressant effects, in major depression it is used with a daily dose of 25 mg. In seasonal affective disorder, it can be effective in very small doses without affecting sleep (43).

In clinical trials for major depression, agomelatine has proven superior efficacy compared to placebos, and has shown equivalent results when compared to conventional antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs) (44).

The advantage of agomelatine is not its better antidepressant effect alone, but its improving effect on sleep together with its antidepressant effect. Indeed, conventional antidepressants often trigger sleep disorders (45).

The first clinical evidence of agomelatine as an anxiolytic medication was observed as a secondary outcome in major depression clinical trials (Kasper et al., 2010). Agomelatine showed increased efficacy over both placebo and active drugs (fluoxetine, sertraline, and venlafaxine) in reducing anxiety symptoms in depression, using the Hamilton Anxiety Rating Scale (HAMA) Since then, there is a continuous interest regarding the properties of agomelatine and its anxiolytic function as an optional treatment for anxiety disorders, especially generalized anxiety disorders (GAD) (40).

3.7. Adverse effects of agomelatine:

Generally, agomelatine is well tolerated by patients. Mild adverse drug reactions observed with agomelatine use (seen in between one and ten patients in 100) are related to somnolence, dizziness, headache, fatigue, and gastrointestinal symptoms like diarrhea (40).

Agomelatine characterized by its different profile of adverse effects compared to SSRIs and Selective Serotonin Nor-adrenaline Reuptake Inhibitors (SNRIs) which are commonly associated to weight gain, sexual dysfunction, and psychomotor agitation (50). In addition, agomelatine use was not associated with discontinuation symptoms after abrupt treatment cessation (46).

Severe adverse reactions were seen, more frequently, with a higher dose of agomelatine. specifically, clinical studies have documented threefold elevations of transaminases enzymes,

particularly in patients taking 50 mg/daily (2.5%), when compared to those taking 25 mg/daily (1.4%). Also, rare cases of hepatic failure were observed (40).

Therefore, agomelatine requires monitoring of liver function, and is contraindicated in patients with impaired liver function and should be avoided in people over 75 years (although no significant effect has been documented in this group) (47).

3.8. Drug interactions

Concomitant treatment of agomelatine with medications that interact with isoenzymes CYP1A2 and CYP2C9/CYP2C19 may decrease or increase plasma concentrations of agomelatine (31).

Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Also, drugs that are potent inhibitors of CYP1A2, such as ciprofloxacin, amiodarone, mexiletine, or zileuton, should be avoided, as well as moderate CYP1A2 inhibitors including estrogens that may also increase the exposure of agomelatine (48).

Conflict of Interest: No conflict of interest.

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