Human Chorionic Gonadotropin and Related Peptides: Candidate Anti-Inflammatory Therapy in Early Stages of Sepsis

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Sepsis continues to be a major cause of morbidity, mortality, and post-recovery disability in patients with a wide range of non-infectious and infectious inflammatory disorders, including COVID-19. The clinical onset of sepsis is often marked by the explosive release into the extracellular fluids of a multiplicity of host-derived cytokines and other pro-inflammatory hormone-like messengers from endogenous sources (“cytokine storm”). In patients with sepsis, therapies to counter the pro-inflammatory torrent, even when administered early, typically fall short. The major focus of our proposed essay is to promote pre-clinical studies with hCG (human chorionic gonadotrophin) as a potential anti-inflammatory therapy for sepsis.

Keywords: inflammation, sepsis, cytokine storm, human chorionic gonadotrophic hormone (hCG), anti-inflammatory

INTRODUCTION

Sepsis

Sepsis is a clinical syndrome characterized by physiologic and biochemical abnormalities associated with organ injury caused by dysregulated host responses to infection (and or inflammation) (1). Sepsis is typically associated with multiple organ failure and a high rate of morbidity and mortality (2, 3). The World Health Organization (WHO) reports over 30 million cases in the world every year with approximately 6 million deaths (4). In the United States, 1.7 million adults develop sepsis each year associated with 270,000 deaths (5). Death rates continue to increase (6). Hospitalizations are often long, often with slow and incomplete recoveries. Prolonged or permanent disability and death are also common.

Emergence of Sepsis

In the healthy individual, pro-inflammatory molecules are roughly balanced by anti-inflammatory elements. In sepsis, multiple intercellular communication pathways are disturbed leading to elevated and sustained pro-inflammatory agents, both helping and harming the host. In about two-thirds of patients with sepsis, infection will be recognized as a dominant cause (7). In the other
third of the patients, no infection is detected; the sepsis is
ascribed to one or more non-infectious inflammatory disorders
e.g., pancreatitis, burns, severe trauma, head injury, or ischemia-
reperfusion (1, 8).

Early in the course of sepsis when infection is uncertain,
clinicians typically (i) culture multiple sites, (ii) immediately
initiate treatment with multiple broad spectrum antibiotics (iii)
while awaiting culture results. Often antibiotic treatment
increases the in vivo dominance of pro-inflammatory
messenger molecules.

A major expected but undesirable consequence of broad-
spectrum antibiotic therapy is a reduction in the host’s native
microbes, especially those of the intestines. This reduction
includes their number, range of species (i.e., diversity), and their
production of molecules of metabolism and intercellular
communication. Disruption of the microbiota can significantly
alter the host’s immune system (9). Under normal circumstances,
the intestinal microbes produce more anti-inflammatory agents
relative to pro-inflammatory messenger molecules maintaining
peaceful balance (“pax intestinalis”) (1). With the use of
antibiotics, the patient’s endogenous microbes that usually
supply anti-inflammatory messengers are markedly diminished,
further promoting the pro-inflammatory dominance.

OVERALL VISION

Our long-range proposal is to provide anti-inflammatory
peptides to patients with sepsis as soon as they are started on
antibiotics to promote the balance between pro-inflammatory
and anti-inflammatory messenger molecules to improve
outcomes. We propose to use well-studied hormones and their
analogs, individually and in unison with mice treated with
broad-spectrum antibiotics, likely to suffer from sepsis. Our
menu of experiments will include microbe-induced sepsis with
one organism, (e.g., pneumococcus), and multiple organisms
(e.g., cecal ligation and puncture). We also plan to study sterile
(microbe-free) sepsis (e.g., post endotoxin or post recovery from
sepsis) (Figure 1).

This manuscript will catalog data that leads us to hypothesize
that human chorionic gonadotropin (hCG) and its relatives from
mammalian and microbial sources may provide benefits when
administered early in sepsis. One significant advantage that will
permit speedy progress with hCG is the vast experience with its
use in laboratory animals and humans, as well as its long-
standing approval by the FDA for multiple uses in humans.

HISTORY OF HUMAN CHORIONIC
GONADOTROPIN

hCG was discovered after decades of extensive research by many
pioneers. In 1920, Hirose demonstrated that placental extracts
stimulated ovulation in rabbits and guinea pigs (10, 11) (see
Table 1). Seven years later, Aschheim and Zondek reported
that the urine of pregnant women contained a substance that
first appears in significant amounts in the urine shortly after
fertilization (15). When this substance was injected into
immature mice, it induced precocious sexual maturity i.e.,
follicular maturation, hemorrhages into follicles and
luteinization of follicles in their ovaries (12–17). This discovery

![Figure 1](https://www.frontiersin.org)
eventually led to the development of a rapid urine test for pregnancy (15, 18–21). In 1929, Zondek discovered that the pituitary gland secreted two hormones that stimulated gonads: Prolan A and Prolan B which became follicle stimulating hormone (FSH) and luteinizing hormone (LH) respectively. Fourteen years later in 1943, Seegar-Jones and colleagues demonstrated that the substance isolated from urine of pregnant women was actually produced by giant syncytiotrophoblast cells of the placenta, not by pituitary gland (12, 14).

Abundant research over several decades made it possible to isolate more pure and potent forms of hCG. In 1931, a placental extract for the stimulation of ovaries was made commercially available by Organon with the brand name Pregnon (12, 22). In 1932, the name was changed to Pregnyl to avoid resemblance with another trademark. hCG preparations are still available today under the trade name Pregnyl. At first, biological activity of hCG extracts was calibrated in animal units such as “rat units.” In 1939, the League of Nations introduced the international unit (IU) that was a new global standard unit of hCG, which greatly increased the reproducibility of the purified forms (13, 23, 24). Purified hCG was extracted from urine for the first time in the 1940s (13, 23, 24). Later in 2000, recombinant hCG preparations became available (13). Currently, urinary and recombinant hCG preparations are widely available from several commercial sources (25), as they are commonly used in the management of infertility and prepubertal cryptorchidism, as well as for stimulating testosterone production in hypogonadal men.

**THE GLYCOPROTEIN HORMONE FAMILY**

The glycoprotein hormone family in mammals has four closely related entities, chorionic gonadotropin (CG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). CG is mainly produced by placenta while LH, FSH, and TSH are mainly produced by pituitary cells (26). Each glycoprotein hormone consists of one α-subunit and one β-subunit that are non-covalently associated (27). The α-subunits of all four hormones are identical (28); a free unbound α-subunit does not have any known independent biological function (29, 30). The β-subunit of the four hormones give biological specificity to each hormone (31) and share some homology in their amino acid sequences (26); CG and LH both bind to the same receptor known as the luteinizing hormone chorionic gonadotropin (LHCG) receptor. FSH binds to FSH receptor and TSH binds to TSH receptor (28, 32, 33). All three receptors are G-protein-coupled to post-receptor pathways (32).

Figure 2A shows that the lengths of the β-subunits vary. Also note that human CG and equine CG each have a unique C-terminal addition that makes them the largest molecules in the family (26, 35) (See Figures 2A, B).

**HUMAN CHORIZONIC GONADOTROPIN**

Unique among the glycoprotein hormones, hCG is mainly produced by syncytiotrophoblast cells of placenta which are the main source of hCG found in the blood and excreted in the urine (36). In early pregnancy, it contributes to the maintenance of the corpus luteum (37, 38), which in turn provides progesterone that is essential for successful pregnancy progression.

**Structure of hCG**

Like the other hormones in this family, hCG is composed of one α-subunit and one β-subunit (39). The α-subunit of hCG contains 92 amino acids with two N-glycosylation sites. It is encoded by a single gene, CGA that is located on chromosome 6q21.1-23 (40). The β-subunit of hCG contains 145 amino acids with two N-glycosylation sites and four O-glycosylation sites. It is encoded by six non-allelic genes (abbreviated CGB) clustered on chromosome 19q13.3 (CGB1, CGB2, CGB3, CGB5, CGB7 and CGB8) (28). The coordination of the six genes and how these six genes lead to the production of one protein are not yet well defined. The α-subunit and β-subunit are extensively intertwined, held together by non-covalent hydrophobic and ionic interactions. The C-terminus of the β-subunit wraps around the α-subunit which is important for subunit assembly. The details of the extensive interface give hints of how α-subunits interact with and associate with the β-subunits of different hormones (31).

**Strength of Binding to the Receptor**

In terms of electrostatic charge and strength of binding to receptor, the hCG’s surface electrostatic potential is positive at or near the receptor-binding interface of hCG receptor and negative on the opposite side. The stronger positive charge yields tighter binding; the less positive charge provides weaker binding. Negatively charged residues in the hCG receptor lower its affinity for binding (31).

**Size and Weight of hCG**

In terms of size and weight, hCG is the largest and heaviest in the mammalian glycoprotein hormone family (28, 40–45). Its β-subunit has a C-terminus with a 31-amino acid extension as well as four additional carbohydrate moieties (46). Together these make hCG a substantially larger molecule than the other mammalian glycoprotein hormones (31) (Table 3 and Figure 3).

**Cells Producing hCG**

Cells in the placenta produce nearly all of the hCG. Small amounts of hCG can also be found in human tissues other
than placenta e.g., liver, kidney, and lung (48). Unlike placenta, these tissues do not secrete hCG into blood. The function of hCG produced by the non-placental tissue is not known. Typically, non-placental normal human pituitary cells do secrete low levels of hCG into blood during the middle of menstrual cycle (49). It mimics LH actions in the menstrual cycle (50), but the specific function of pituitary hCG is not well understood (48). Multiple primary malignant cells such as those from colon cancer, ovarian cancer, and breast cancer also secrete hCG (46, 51–54). This is considered to be a sign of poor prognosis, possibly because the free β-subunits prevent apoptosis of malignant cells, thereby enhancing the malignant cell growth (50).

**FIGURE 2** | (A) Amino acid sequences of the β-subunits of glycoprotein hormones (34): The shortest β-subunit in the family is bovine FSH-β consisting of 111 amino acids; the longest β-subunits in the family are of equine LH-β and equine CG-β consisting of 149 amino acids (equine LH-β & equine CG-β are identical) (26). h = human, e = equine, o = ovine, b = bovine, p = porcine CG = chorionic gonadotrophin; LH = luteinizing hormone; FSH = follicle-stimulating hormone; TSH = thyroid stimulating hormone. (B) Homology of β-subunits of glycoprotein hormones. Exceptionally, the amino sequences of equine LH-β and equine CG-β are identical (26). Human LH-β and human CG-β are about 70% homologous. Ovine LH-β and ovine FSH-β are about 34% homologous. Bovine LH-β and bovine CG-β are about 30% homologous. H, human; e, equine; o, ovine; b, bovine; p, porcine; CG, chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone.

**FIGURE 3** | Glycoprotein hormone molecule (73). hCG has the largest size of the glycoprotein hormones due to carboxy-terminal addition. The α-subunits are represented by red strand; the β-subunits are represented by blue strand; carbohydrate chains are represented by light blue balls. Figure from SpringerLink (73) permissible to reuse under a CC-BY 4.0 license.
GONADOTROPIN FROM MICROBES

Peptides Secreted by Microbes

The search for peptides secreted by microbes similar to mammalian hormones started more than a half century ago. Our lab group reported TSH-like material in Clostridium perfringens as well as insulin-related material in Escherichia coli, and melanocortin-related material in E. coli and other microbes. Other groups found insulin-related materials, somatostatin-like materials, calcitonin, and calcitonin (55–57). Several strains of bacteria were found to release neurotensin (58). Recently, we characterized a melanocortin-like peptide secreted from E. coli (MECO-1) that has anti-inflammatory effects (59). MECO-1 is a 33-amino acid peptide released by E. coli that is homologous to the C-terminus of the E. coli elongation factor-G (EF-G); it is similar to alpha melanocyte-stimulating hormone homologous to the C-terminus of the E. coli elongation factor-G (EF-G). MECO-1 showed greater anti-inflammatory properties than α-MSH to protect mice from lethal doses of LPS or sepsis induced by cecal ligation and puncture (CLP) (59); possibly MECO-1 has longer survival in vivo (Figure 4).

hCG-Related Peptides in Microbes

Initially thought to be produced only in mammals and other chordates, CG-related peptides have been reported in multiple microorganisms e.g. Staphylococcus species, Corynebacterium ulcerans, Eubacterium lentum, Escherichia coli, Stenotrophomonas (Xanthomonas) maltophilia, and Progenitor cryptocides. Some species of Streptococcus, and of Candida express mRNAs and proteins that resemble transcripts and proteins of CG. Some of the microbe-derived peptides have been shown to produce as well as secrete gonadotropin-like peptides (41, 46–49, 51–54, 60–69).

In the 1970s, several anaerobic and aerobic bacteria isolated from patients with a range of malignant tumors (including colon, ovary, breast and lymph node) were found to release hCG-like material when assayed for the β-subunit of hCG (51, 54). hCG-like substances were reported in cancer patients. hCG was also detected in some bacteria and yeast from patients independent of the presence of a tumor (36). hCG-like material was detected not only in microbes that were commonly found in humans such as Staphylococcus epidermidis, S. hominis, S. haemolyticus, and Candida albicans, but also in bacteria that are less common residents of human microbiota (68, 70).

Xanthomonas maltophilia is an uncommon but emerging nosocomial pathogen that is usually resistant to widely used antibiotics (71). LHCG-binding sites were found in X. maltophilia (68). Because these lack complete functional units, some authors have hesitated to call them receptors. While both human LH and hCG bind to LHCG-low-affinity binding sites, only hCG (not human LH) can bind to LHCG high-affinity binding sites. Other glycoproteins such as LH, FSH, and TSH do not bind to them (61, 68). Hormone binding to high-affinity LHCG-binding sites is known to stimulate cell proliferation and changes in cell morphology (72). These changes are stimulated by hCG, LH and Xanthomonas CG (72). The entire gene of choriionic gonadotropin has been isolated from X. maltophilia (Xanthomonas CG), was completely sequenced and showed homology to human CG and human LHCG receptor (46, 68)(See Table 2). The molecular weight of fungal CG is greater than the microbial CG which is greater than mammalian CGs (28, 46, 47) (See Tables 2, 3 and Figure 5).
increased production of pro-inflammatory cytokines such as interleukin 2 (IL-2), interleukin 6 (IL-6), and TNF-α (76, 77). Remarkably, these inflammatory changes do not appear to harm them otherwise (76). One of the protective agents is hCG (77), which activates macrophages directly, especially their innate immune functions. Macrophages produce oxygen radicals for the mother’s defense against microorganisms and enhance phagocytic activities to clear apoptotic cells that are essential for resolution of local inflammation (77). In pregnancy, apoptosis is important for tissue remodeling and placental invasion during implantation (78, 79). Fas and Fas ligand (FasL) are involved in regulation of cell death (76). FasL mediates apoptotic processes to enhance placental invasion during implantation (79). Macrophages engulf the apoptotic cells, thereby preventing or retarding the potential pro-inflammatory actions generated by apoptotic cells (78) (Figure 6).

hCG, with interferon gamma (IFN-γ)-primed macrophages, significantly increases nitric oxide (NO) production and reactive oxygen species (ROS) that are cytotoxic for microorganisms including fungi, protozoa, bacteria and viruses. These free radicals offer crucial protection against microorganisms potentially dangerous for both mother and fetus (81). These functions of macrophages are vital to the maintenance of pregnancy and important to understand the “harmless” controlled state of sterile inflammation in pregnancy as well as hCG’s therapeutic benefits in acute inflammation (77).

In early stages of pregnancy, hCG contributes to maternal-fetal tolerance by increasing the migration of regulatory T cells (Tregs) into the maternal-fetal interface, thereby increasing Tregs in the lymphatic organs and circulation. Tregs promote activities in vivo that increase the production of anti-inflammatory cytokines such as IL-10 and of TGF-β (82, 83), which in turn dampen TNF-α, a pro-inflammatory cytokine. hCG also enhances a tolerogenic phenotype of bone marrow-derived dendritic cells (DCs) (74, 82, 84, 85). Zhou et al. have confirmed that for successful in vitro fertilization (IVF) Treg expansion and successful pregnancy are positively associated with increasing numbers of Tregs in the peripheral blood (86).

Macrophages and dendritic cells are involved in the innate immune response. Although macrophages are stimulated by foreign entities, they are not able to initiate a primary immune response. Table 2

| TABLE 2 | Homology between bacterial CG and human CG. |
| Homology to human | Location of homology |
|------------------|----------------------|
| Xanthomonas CG   | 46% homology to human CG |
| LHCG binding site in Xanthomonas | 73% homology to LHCG receptor |
| The body of β-subunit in amino acids 1761-1994 and 25-aa region of the C-terminus | The human LHCG receptor |

The entire gene of chorionic gonadotropin isolated from Xanthomonas was completely sequenced and showed 46% homology in the body of hCG β-subunit in amino acid 1761-1994 and in the 25-aa region of the carboxyl-terminal of hCG (42). The DNA sequence of the LHCG-binding site was even more similar to the human receptor, with 73% homology (68).

Table 3

| TABLE 3 | Human CG vs microbial CG (Xanthomonas and Candida Chorionic Gonadotropin). |
| Molecular Weight | Size (Base Pairs) |
|------------------|------------------|
| Human CG         | 37 kDa 711 bps   |
| Xanthomonas CG   | 48 kDa 1362 bps  |
| Candida CG       | 68 kDa           |

In terms of size and weight, microbial CGs are larger than human CG. The molecular weight of Candida CG is 68 kDa compared to 48 kDa of Xanthomonas CG and 37 kDa of human CG. Xanthomonas CG has 1362 base pairs in its sequence that can be converted to 454 amino acids (1362 bp/3 = 454 AAs), and hCG has 711 base pairs that can be converted to 237 amino acid that calculated from the addition of 92 of α-subunit and 145 of β-subunit (28, 46, 47).
Dendritic cells, acting as antigen-presenting cells (APCs), can initiate a primary immune response by stimulating naive T cells (88). This is the interface between the innate and adaptive immune responses promoted by dendritic cells (87, 89).

hCG regulates dendritic cell function by enhancing maternal-fetal immune tolerance (85) (Figure 7).

**Tempering Inflammation With hCG**

Many studies have demonstrated the anti-inflammatory influences of hCG. For example, Wan et al, found that in C57BL/6 female mice with thioglycolate (TG)-induced peritonitis, hCG pre-treatment diminished inflammation-induced cell death and decreased pro-inflammatory cytokine levels including IL-6, TNF-α, PTX3, CCL3, and CCL5 (77) (Figure 8).

BALB/c mice with acute liver injury induced by anti-Fas antibody (Jo 2) and agonistic CD95-antibodies had significantly reduced levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) when also treated with hCG. Mice treated with hCG also showed less CD4+ T cell infiltration and fewer apoptotic hepatocytes, confirming the effectiveness of hCG as an anti-inflammatory agent (90).

Signs of rheumatoid arthritis (RA) were induced in rats by the injection of streptococcal cell wall (SCW). Non-pregnant rats showed joint swelling, pro-inflammatory cell infiltration, increases in TNF-α, IL-6, IL-1β, NO, and inducible nitric oxide synthase (iNOS). hCG administration reduced signs of arthritis (91).

**Anti-Inflammatory Effects in Humans**

Reduced symptoms of autoimmune diseases including rheumatoid arthritis (RA) and Sjogren syndrome (SS) have been reported during pregnancy (92, 93). Hazes et al. found a decrease in risk of RA among women who have been pregnant compared to nulligravid women [odds ratio was 0.49 (0.27-0.91)]. An early first pregnancy is associated with lower risk of RA (92). The contribution of hCG to this amelioration was suggested by several investigators (92, 93).
FIGURE 7 | The role of dendritic cells; linking innate immunity and adaptive immunity. [Reproduced from (89)]. One key role of dendritic cells is linking innate immunity to adaptive immunity. When confronted with microbial antigens, dendritic cells (DCs) mature and migrate into draining lymph nodes where they present antigens to naïve T lymphocytes. Different pathogens trigger distinct dendritic cell maturation profiles and lead to the polarization of different T-cell subsets. Then, the adaptive immune response is modulated to match the nature of the pathogen (89). Ag, antigen; CTL, cytotoxic T cell; DC, dendritic cell; PRRs, Pattern recognition receptors; PAMPs, Pathogen associated molecular patterns. Figure from Intechopen (89) permissible to reuse under a CC-BY 4.0 license.

FIGURE 8 | hCG pre-treatment reduces the level of IL-6 and TNF-α in peritoneal lavage fluid (77). C57BL/6 mice were injected intraperitoneally with hCG or PBS. One hour later, TG was intraperitoneally injected after 2 h, 4 h, 24 h (Day 1), and 72 h (Day 3). On Day 5, mice were sacrificed, and peritoneal lavage fluid was collected, and cytokine measured. Upon hCG pretreatment of TG-induced peritonitis, decreased IL-6 (A) and TNF-α levels (B) at 2 h and 4 h and a higher IL-10 level (C) at 72 h were observed, whereas IL-12p40 remained unchanged (D); n = 15. Kinetic data depicted are from a separate representative experiment with five mice per group (A, B). *P < 0.05; **P < 0.01; ***P < 0.001.
SYNTHETIC PEPTIDES RELATED TO HCG: LQGV, AQGV, AND LAGV

Van den Berg et al. concluded that the anti-inflammatory effects of hCG are derived from peptides located in the hCG β-subunit such as LQGV, AQGV, and LAGV (94–97). Using rats with hemorrhagic shock they demonstrated the anti-inflammatory effects of these peptides. Hypotension (a mean arterial pressure of 40 mmHg) was maintained for 60 minutes. Groups of rats received either 5 mg/kg of LQGV, AQGV, LAGV, or normal saline (94). Administration of LQGV, AQGV, and LAGV prevented the release of IL-6 and TNF-α into the plasma and attenuated the rise of IL-6 and TNF-α mRNA transcript levels in the liver. LQGV treatment also attenuated the accumulation of neutrophils in the liver and the rise of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels while AQGV and LAGV treatment did not (94, 96).

AQGV

Khan and his colleagues studied AQGV, an oligopeptide related to hCG-β, as an anti-inflammatory agent (97). They found that AQGV prevented mortality in mice with induced renal ischemia-reperfusion injury more effectively than other oligopeptides related to hCG-β by lowering neutrophil influx to the kidney, decreasing apoptosis, reducing proinflammatory cytokines such as TNF-α, INF-γ, IL-6 and IL-10, and increasing tubular epithelial cell proliferation (97) (Table 4).

LQGV

A number of groups studied LQGV, another hCG-β related tetrapeptide, as a treatment for sepsis (94, 96, 98–100). The LQGV, leucine-glutamine-glycine-valine is present in loop 2 of the hCG-β subunit (96). Khan’s group found that the LQGV peptide showed a protective effect in mice with lethal LPS-induced septic shock and in rhesus monkeys with E. coli-induced septic shock (99). Following an injection of a lethal dose of LPS or E. coli to induce septic shock, mice and monkeys received LQGV or phosphate-buffered saline (PBS). The mice and monkeys that received LQGV demonstrated significantly improved hemodynamic parameters, improved sickness scores, and higher survival rates (99). LQGV treatment also showed anti-inflammatory effects on mice with CLP-induced sepsis. Van den Berg’s group induced sepsis in C57BL/6 mice with CLP and administered either LQGV or PBS as control to assess the anti-inflammatory effects of LQGV. Results demonstrated that LQGV treatment increased the survival rate up to 50% from 20% during acute phase of sepsis. LQGV treatment also decreased CLP-induced systemic cytokines (96).

CONCLUSION

hCG is a major pregnancy hormone that belongs to the glycoprotein family. The well-known functions of hCG are related to pregnancy, such as the maintenance of the corpus luteum and angiogenesis of uterine vasculature. hCG is used in infertility treatment, prevention of postmenopausal symptoms and induction of testosterone production in hypogonadal men. Peptides similar to this hormone have been detected in microorganisms such as viruses, bacteria, protozoa, and fungi. The study of hCG recently has been expanded beyond its role as a pregnancy hormone to include studies demonstrating anti-inflammatory capabilities.

A number of pre-clinical and clinical studies have clearly demonstrated that the β-subunit of hCG and its related oligopeptides have anti-inflammatory properties. hCG and its related peptides show promise in the treatment of inflammatory diseases and sepsis to mitigate organ failure and reduce mortality. Further clinical studies are warranted to establish its role as an anti-inflammatory agent, alone and in concert with other anti-inflammatory agents.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication. Also note that SYK, SFM, SP, NM and JR substantially contributed to the conception and design of the article and interpretation of the relevant literature. BLu, DL, CNM, HY and JR added critical intellectual content to the manuscript and can be considered experts on the topic. All authors including MA, BLo and SAK provided critical feedback and helped shape the research and analysis.

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