Clinical Use of Pentraxin 3: A Review

Ali Kemal Erenler\textsuperscript{1*}, Oğuzhan Yücel\textsuperscript{2} and Ahmet Baydın\textsuperscript{3}

\textsuperscript{1}Hitit University Çorum Education and Research Hospital, Çorum, Turkey.  \\textsuperscript{2}Samsun Education and Research Hospital, Samsun, Turkey.  \\textsuperscript{3}Samsun Ondokuzmayıs University, Samsun, Turkey.  
*Corresponding author E-mail: akerenler@hotmail.com.

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Pentraxin 3 (PTX3) is a novel marker of the acute-phase inflammatory response, belonging to the PTX protein family. It also plays a role in innate immunity. It is known to be produced at the site of infection or inflammation by macrophages, monocytes, dendritic cells, and tissue cells. Increased levels of PTX3 in the circulating blood have been found to be involved in many pathologies such as coronary artery, respiratory system, renal, hematological, neurological and inflammatory diseases. In this review, we aimed to clarify the biochemical structure of PTX3 and reveal its etiological and diagnostic importance in diseases frequently seen in the Emergency department.

**Key words:** Pentraxin, critical care, emergency medicine

**INTRODUCTION**

The search for an ideal marker in all kinds of diseases is an ongoing challenging issue for the scientists. Biomarkers are measurable and quantifiable biological parameters that can have an important impact on clinical situations. Ideal biomarkers are those that are associated with disease clinical endpoints in observational studies and clinical trials, and in some cases, they may even be used as surrogate endpoints. Biomarkers must also be both independent of established risk factors and recognized to be a factor in the disease for which they are a marker (Pearson et al., 2003).

Pentraxins are a family of evolutionarily conserved proteins. They are divided into short (25 kDa) and long (40-50 kDa) pentraxins on the basis of their primary structure (Tamura et al., 2012; Lee et al., 2010). While short pentraxins like C-reactive protein (CRP) are produced from the liver, long pentraxins like pentraxin 3 (PTX3) are highly expressed in the heart (Lee et al., 2010). Pentraxin synthesis is stimulated in endothelial cells, macrophages, myeloid cells, dendritic cells by cytokines and endooyxins such as bacterial products, interleukin–1, and TNF (Inoue et al., 2012). Pentraxin 3 release appears to be a specific response to vascular damage, indicating that PTX3 may provide more explicit information on development and progression of atherosclerosis than non-specific markers, such as CRP (Jenny et al., 2009).

PTX3 is considered to play an important role in the regulation of innate immunity to pathogens and inflammatory reactions. Similar to CRP, PTX3 has been reported to be a biomarker for a number of different clinical conditions such as cardiovascular disease and death, atherosclerosis, non-alcoholic steatohepatitis, pulmonary infections and lung injury, systemic lupus erythematosus, systemic sclerosis preeclampsia, and lung cancer. In contrast to CRP that mainly is synthesized in the liver, PTX3 is produced at the site of infection or inflammation by macrophages, monocytes, dendritic cells, and tissue cells (Akerfeldt and Larsson, 2011). Activation stimuli which control PTX3 synthesis...
and release can be enumerated as follows: (1) proinflammatory cytokines (IL-1β, TNF-α), (2) TLR agonists, namely lipopolysaccharide (LPS), (3) distinct microbial moieties (OmpA, lipoarabinomannans), and/or (4) some intact microorganisms (Kunes et al., 2012). In this review, we aimed to investigate the structure and the clinical utility of PTX3 in specific diseases.

**STRUCTURE OF PENTRAXIN 3**

The human PTX3 gene is localized on the chromosome 3q band 25. It is composed of three exons, the first two of which encode for the signal peptide and the N-terminal domain (amino acids 18–179), respectively. The third exon encodes for the C-terminal domain featuring the pentraxin signature (amino acids 179–381) (Bottazzi et al., 1997). Pentraxin 3 promoters contain enhancer-binding elements which, during proteosynthesis, fine-tune final impact of PTX3 on its target structures. The most prominent ones are activator protein–1 (AP–1), nuclear factor-kappa B (NF-kB), and selective promoter factor 1 (SP1). Briefly, AP–1 enhances basal transcription of PTX3, whereas the NF-kB binding site is operative in the response to inflammatory cytokines TNF-α and/or IL-1β. Tissue-specifically, the above-mentioned transcription factors are complemented, in their proteosynthesis-modulating activities, by enzymatic biochemical pathways. In lung epithelial cells challenging acute inflammation, PTX3 mRNA as such is induced by TNF-α; nevertheless, PTX3 protein generation itself does not require consequent NF-kB transcription. Instead, PTX3 is manufactured by way of the c-Jun N-terminal kinase pathway. In endothelial cells, expression of PTX3 is readily induced by TNF-α and IL-1β (Kunes et al., 2012). The pentraxins form a superfamily of multifunctional proteins which have been conserved in phylogeny from arachnids to mammals. The pentraxin superfamily is distinguished by the presence in their C (carboxy)-terminal region of a ~200 amino acid domain containing a highly conserved motif of 8-amino-acid sequence, which has been named the pentraxin signature (HxCxS/TWxS, where x is any amino acid). Based on the primary structure of the promoter, the pentraxins branch off into two groups: the short constituents and their long counterparts (Bottazzi et al., 2010). Pentraxin 3 is the first identified long pentraxin, consisting of a C-terminal pentraxin module coupled with an unrelated N-terminal domain. Pentraxin 3 is structurally related but distinct from classic pentraxins. It differs from the classic short pentraxins in terms of gene organization and localization, ligand recognition, producing cells, and inducing signals (Inoue et al., 2007). Immature myeloid dendritic cells were supposed to be the prevailing cellular population capable to produce PTX3. However, stimulus-induced PTX3 has been detected in other cellular populations, such as the monocytes/macrophages, smooth muscle cells, kidney epithelial cells, synovial cells, chondrocytes, adipocytes, alveolar epithelial cells, glial cells, fibroblasts, and endothelial cells (Introna et al., 1996). In endothelial cells, expression of PTX3 is readily induced by TNF-α and IL-1B. Thereafter, an acute cellular alteration sets in, in which the endothelial cell is converted from a quiescent, anti-inflammatory phenotype, to a procoagulant and proinflammatory cellular surface (Kunes et al., 2012).

**Pentraxin 3 and atherosclerosis**

Immunological and inflammatory processes play an important role in the development of atherosclerosis (Knoflach et al., 2012). It was reported in a murine model that PTX3 accumulates during atherosclerosis progression (Norata et al., 2009). In a study, Inoue et al. investigated the origin of the PTX3 from the ruptured plaque or a systemic process and cells that release PTX3. Blood samples were taken using an aspiration catheter from the site of the ruptured plaque and from the aorta during acute coronary interventions in 118 patients with acute coronary syndrome. These samples were analyzed for PTX3, and brain natriuretic peptide (BNP) was used as a control. Aspirated thrombi from 32 patients with acute myocardial infarction (AMI) were examined by histological staining (Daida, 2011). Immunohistochemical examination of aspirated thrombi demonstrated the infiltration of neutrophils expressing PTX3 (Savchenko et al., 2008). This study found that almost 70% of the neutrophils expressed PTX3 in the thrombus. Their findings indicated that plaque volume or endothelial dysfunction may not be important to increase plasma PTX3 level but PTX3 originates from neutrophils at the site of plaque rupture in the coronary artery of patients with ACS (Daida, 2011). In a study, PTX3 levels were found to be independently associated with prevalent cardiovascular diseases but there was no association with elevated intima-media thickness, a precursor lesion of atherosclerosis. It was also found that PTX3 level correlated with the severity of carotid and femoral atherosclerosis and was highest in individuals with multiple vascular territories affected. It was also reported that PTX3 serum level was a marker of advanced and symptomatic but not early atherosclerosis in humans. When compared to CRP, PTX3 predicted prevalent cardiovascular disease better, had fewer associations with other vascular risk conditions and may be more specific for vascular wall inflammation (Knoflach et al., 2012).

In concordance, recently it was reported that patients with hypertension had higher plasma levels of PTX3 and its mediators P-selectin and matrix metalloproteinase-1 than normotensive subjects which indicates that these might be novel biomarkers that predict the onset of vascular dysfunction in hypertensive patients (Carriozzo et al., 2015).
Pentraxin 3 and coronary artery diseases

Every year in the United States, 2.5 million patients are admitted to a hospital with an ACS, two thirds of whom are eventually diagnosed with UAP or non–ST elevation MI (Yamashina et al., 2003). Onset of acute coronary syndrome (ACS) involves rupture or erosion of atherosclerotic plaques in coronary arteries. Although biomarkers for ischemic myocardial damage, such as troponin-T (TnT) and heart-type fatty acid binding protein (H-FABP), have been clinically utilized to diagnose ACS, diagnostic sensitivity and specificity for ACS, especially at the earliest stage, remain insufficient (Libby, 2001; Falk et al., 1995). To make a diagnosis of ACS, biochemical markers and the resting ECG are key components for the proper assessment of a patient with a suspected ACS. The biochemical markers of myocardial necrosis, predominately CPK, as well as troponin T, are also essential in the diagnosis and prognosis of patients with ACS. Because cardiac troponins are not detected in the blood of healthy individuals and are cardiac specific, they are sensitive and specific for myocardial necrosis. But because UAP does not have any cardiac necrosis theoretically, neither CPK nor troponin T levels are elevated. Furthermore, some studies have suggested that 5 to 10% of patients with chest pain and exhibiting a normal ECG will subsequently be diagnosed with unstable angina (Braunwald, 2004). Therefore, there is a need to establish an assay system to predict unstable angina pectoris (UAP). Lately, many studies investigated the utility of PTX3 in the early diagnoses of Acute Coronary Disease (ACD). As we know that PTX3 is made in response to primary proinflammatory signals (bacterial products, IL-1, and tumor necrosis factor [TNF]), but not IL-6) by diverse cell types, predominantly macrophages and vascular endothelial cells, but not liver, Inoue et al. hypothesized that PTX3 levels might more directly reflect the inflammatory status of the vasculature. They assessed the clinical utility of PTX3 in CAD. After developing a highly sensitive ELISA system, they found that PTX3 levels were elevated in patients with UAP. They also reported that PTX might be a good predictive marker for ACS. In their study, PTX3 was found to be an exceptional marker fitting all the established criteria of an ideal biomarker to detect ACS: (1) the ability to standardize the assay; (2) independence from established risk factors; (3) association with CAD incidence; (4) the presence of population norms to guide interpretation of results; (5) ability to improve the overall prediction beyond that of traditional risk factors. They used different mouse monoclonal antibodies against human PTX3 for capture and signal to establish a high sensitivity ELISA system for PTX3. In patients with atherosclerotic lesions receiving treatment (so called, activated inflammatory status), plasma PTX3 levels increased (Inoue et al., 2007).

Peri et al. (2000) reported serum PTX3 as an early indicator of AMI in humans and with no correlation between serum concentrations of PTX3 and CRP. Peri et al. (2000) reported their results from a cohort of 37 patients who had presented with an AMI. The authors showed that in these patients, plasma levels of PTX3 peaked as early as ~6 hours after the onset of chest pain. Thus, maximal concentration of PTX3 was available much earlier than that of CRP which is achieved after ~48 h (Peri et al., 2000). Ustundag et al. (2011) investigated the comparative diagnostic accuracy of serum levels of neutrophil activating peptide–2 and pentraxin–3 versus troponin-I in ACS. Consecutively eighty-three patients with sudden chest pain admitted to Dicle University Emergency Department within the first six hours of symptom onset were included in this study. Pentraxin 3 levels were found to be considerably higher compared with control group in all three types of ACS (USAP, STEMI, and NSTEMI). They also found that the sensitivities of all four markers were similar, but PTX3 was indisputably superior to the others within the first three hours after symptom onset. When compared to the other mentioned markers, they concluded that the most useful marker to the emergency physician in diagnosing ACS would be PTX3 (Ustundag et al., 2011). Similar results were obtained when PTX3 levels were compared with TnT and (Heart type fatty acid binding protein) H-FABP levels in patients with ACS. Kume et al. (2011) reported that diagnostic values of PTX3 were also evaluated in ST-elevation ACS (STE-ACS) alone, comparing them with those of TnT and H-FABP, by exclusion of non-ST-elevation ACS (NSTEMI) patients. In their study, sensitivity and specificity of PTX3 for the diagnosis of ACS appeared to be higher than those of TnT and H-FABP. In a study by Saygi et al. (2012) they investigated 17 patients with non ST elevation ACS and 22 patients with stable angina who have undergone coronary stenting. Blood samples were obtained serially from patients to measure PTX3 levels at admission, at 8 h and 24 h after stenting. They found strong correlation between 24 h serum PTX3 levels and GRACE scores in patients with non ST elevation ACS underwent coronary stenting. Eighth hour mean PTX3 level was significantly higher in ACS group. However, surprisingly, no correlation was observed between 8th hour PTX3 levels and GRACE scores in ACS patients (Saygi et al., 2012). In another study with patients with ST-elevated MI undergoing PTCI, high PTX3 levels on admission were found to be associated with increased cardiovascular mortality (Akgul et al., 2015). It was also found that high PTX may help predict the severity of coronary disease (Nerkiz et al., 2015). These results reveal that PTX3 is not only associated with the presence of CAD but also has a value in prognosis and severity prediction in MI patients. Similarly, a recent research by Liu et al. (2015)
demonstrated a positive correlation between PTX3 levels and severity of coronary lesions (Liu et al., 2015). In a study, Lee et al. determined that the serum PTX3 concentration was significantly correlated to Troponin T and the degree of Killip class, in CHF, among the parameters determining the GRACE risk scores, and the degree of Killip class was independently associated with an incremental change in the serum PTX3 level (Lee et al., 2010). Suzuki et al.(2008) demonstrated that the concentration of plasma PTX3 levels was significantly higher in patients with heart failure than in control subjects and increased with advancing New York Heart Association (NYHA) functional class, especially in severe patients with heart failure and NYHA class III or IV (Suzuki et al.,2008). In a cohort study by Dubin et al. (2012), found in persons with stable CHD that PTX3 is significantly associated with all-cause mortality, CV events, and incident HF independently of demographics, traditional CVD risk factors, and systemic inflammation. They also found that these findings were independent of systemic inflammation, kidney dysfunction, and traditional CV risk factors (Dubin et al., 2012). In a recent study, Norimatsu et al. demonstrated that, when combined with patient's age, PTX3 is an independent risk factor for aortic valve calcification in patients with aortic valve stenosis (Norimatsu et al.,2015).

Pentraxin 3 and respiratory system

Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are characterized by a sudden activation of innate immunity and other inflammatory mechanisms involving the lungs. Several mediators both pro- and anti-inflammatory are involved, particularly in the early phase of the syndrome (Ware and Matthay, 2000). Results of a study by Mauri et al.(2008) showed that plasma PTX3 is substantially elevated in ALI/ARDS patients, up to 2000-fold of the normal value. They reported that in ALI/ARDS patients PTX3 is an early marker of severity which correlates with lung function, systemic organ failure, and outcome (Mauri et al., 2008). In a study, Okutani et al., (2007) determined the effect of mechanical ventilation on PTX3 expression in multiple lung injury models in rats. They concluded that high-volume ventilation increases PTX3 expression in the lung and PTX3 expression in the lung is correlated with the severity of lung injury (Okutani et al., 2007). In addition, Simon et al.(2006) showed how PTX3 gene expression was increased in gravitationally dependent regions in a dog ventilator-induced lung injury model, suggesting that its trigger may be more related to the stresses of opening and collapse rather than over distension. A model of injurious mechanical ventilation implemented in PTX3-deficient mice could finally proof the centrality of PTX3 in ventilator-induced lung injury pathogenesis (Simon et al.,2006). In a study by Tamura et al. (2012), they demonstrated that human PTX3 is a specific biomarker for pulmonary arterial hypertension (PAH), reflecting pulmonary vascular degeneration, especially in patients with connective tissue disease (CTD) (Tamura et al., 2012). Infante et al.(2015) revealed that serum PTX3 values in patients with lung cancer were significantly higher compared with cancer-free heavy smokers. Their results have shown that serum PTX3 might have a potential to be a biomarker of lung cancer in high-risk patients (Infante et al., 2015). Additionally, increased levels of PTX3 in patients with obstructive sleep apnea syndrome were reported (Asiye et al., 2015). In pediatric patients, PTX3 has been shown to reflect severity of lower respiratory infection (Kim et al., 2017).

Pentraxin 3 and nephrology

It is known that chronic kidney disease (CKD) and end stage renal disease (ESRD) are associated with higher PTX3 levels. Higher PTX3 levels are also associated with endothelial dysfunction and proteinuria in stage 5 CKD patients and in patients with type 2 diabetes (Dubin et al., 2011;Tong et al., 2007; Suliman et al., 2008). In IgA nephropathy, serum PTX3 levels were shown to be an independent marker of disease activity because PTX3 is induced by tumour necrosis factor TNF-α at sites of inflammation and within adipose tissue (Lech et al., 2013). It is also known that there is a correlation between anti-PTX3 antibody production and protection from renal immunopathology in SLE patients.

Patients with SLE were shown to have higher levels and prevalence of anti-PTX3 antibodies and anti-PTX3-related peptide antibodies than patients with other autoimmune rheumatic diseases or healthy controls. Anti-PTX3 antibodies were not associated with disease activity but with the absence of glomerulonephritis (Bassi et al., 2010).

Pentraxin 3 expression is increased in the IgA, type I membranoproliferative, diffuse proliferative lupus glomerulonephritis and in membranous glomerulonephritis and focal segmental glomerular sclerosis. Pentraxin 3 is remarkably present in the mesangial, endothelial areas and inflamed interstitium in renal biopsies obtained from patients with these glomerulonephritis (Bussolati et al.,2003). It is also known that PTX3 levels in patients on hemodialysis are significantly higher when compared to healthy subjects (Yigit et al., 2015).

Sjöberg et al. (2015) reported that higher PTX3 levels were associated with lower GFR and independently predict incident chronic kidney disease (CKD) in elderly men and women.

They also reported that inflammatory processes were activated in the early stages of CKD and drive impairment of kidney function. As a result of these findings, they suggested PTX3 as a promising biomarker of kidney disease (Sjöberg et al.,2015).
Pentraxin 3 and hematology

In a study, it was reported that PTX3 predicts complications of febrile neutropenia in haematological patients with AML and NHL, but the decision level differs according to the underlying hematological malignancy (Juutilainen et al., 2011). Pentraxin 3 is a promising biomarker to diagnose septic conditions more rapidly than CRP, because of both its origin and induction by proinflammatory cytokines and bacterial products (Akerfeldt and Larsson, 2011). In a 3 year prospective study, Vanska et al. observed that high levels of PTX3 were associated, already at the onset of fever, with the development of septic shock and bacteremia in neutropenic hematologic patients receiving intensive chemotherapy. PTX3 was not superior to CRP as a biomarker predicting a complicated course of neutropenic fever (Vanska et al., 2011).

Pentraxin 3 and dentistry

Periodontal disease is a multifactorial infectious disease; although the main cause of periodontal disease is the presence of periodontal microorganisms, subsequent progression and disease severity are considered to be determined by the host immune response. In a study, Keles et al. found that levels of PTX3 in gingival tissue were significantly higher in experimental periodontitis group after 10 days. In contrast to their hypothesis, there was no significant difference in gingival tissue PTX3 levels between experimental periodontitis after 40 days and periodontally healthy groups. The difference in the serum levels of PTX3 was not statistically significant between the study groups. The results of their study showed that the concentration of PTX3 in gingival tissue and serum was positively correlated with alveolar bone resorption and with inflammatory cells in epithelium both in experimental periodontitis groups (Keles et al., 2012). The results of this study showed that gingival tissue PTX3 levels were not increased in experimental periodontitis model with 40-day period, contrary to the gingival crevicular fluid findings of Pradeep et al. which reported that concentration of PTX3 in gingival crevicular fluid is increased in proportionately with the severity of periodontal disease (Pradeep et al., 2011).

Pentraxin 3 and neurological diseases

Higher levels of PTX3 as the main component of the pentraxins are associated with increased mortality after ischemic stroke, but the underlying mechanisms are unclear. Based on the mechanism by which CRP plays a role in atherosclerosis development, PTX3 might be related to the development of atherosclerosis because these molecules are members of the pentraxin superfamily (Norata et al., 2010). In mice, it has been shown that PTX3 level increases after experimental stroke (Rodriguez et al., 2014). Besides, key mediator role of PTX3 in angiogenesis and neurogenesis after cerebral ischemia has been reported. It also has beneficial impact on recovery of lateral motor function (Rodriguez-Grande et al., 2015). Ryu et al. (2012) found that PTX3 was a strong, independent predictor of long-term mortality after ischemic stroke (Ryu et al., 2012). In a study by Wang et al. investigated plasma levels of PTX3 in patients with multiple sclerosis (MS) and neuromyelitis optica (NMO). Their results showed a statistically significant correlation between plasma levels of PTX3 and Expanded Disability Status Scale scores in MS and NMO patients during relapse (Wang et al., 2013). In a study Ceylan et al. compared the migraine attack, interictal and control groups regarding the serum levels of PTX-3, CRP, fibrinogen and D-dimer. They found that patients with longer attacks and disease durations have lower serum levels of PTX-3. They also reported that these findings suggested alterations in inflammatory processes along with disease progression (Ceylan et al., 2015).

Pentraxin 3 and surgical procedures

Akerfeldt and Larsson, (2011) investigated the comparison of CRP levels and PTX3 in patients’ undergone surgical procedures. They analyzed the blood samples of 29 orthopedic and 21 coronary bypass patients. The coronary bypass surgery patients had higher CRP and PTX3 than the orthopedic patients at baseline. They reported that this increase was probably due to more advanced cardiovascular diseases in this patient group as cardiovascular diseases are associated with increased levels of both CRP and PTX3. CRP and PTX3 increased in both patient groups 4 days after surgery but had decreased again on day 30. The increase in CRP was much more pronounced than the PTX3 increase (Akerfeldt and Larsson, 2011). Aksungur et al., (2015) have measured PTX3 levels in both acute cholestitis and control groups. Even though a statistical significance could not be determined, when compared to the control group, PTX3 levels were increased in patients with the female gender, in gangrenous cholecystitis, in patients having morbidity and mortality. In the same study, PTX3 levels were statistically significant in terms of elderly patients and increased duration of hospital stay (Aksungur et al., 2015).

Pentraxin 3 and inflammatory diseases

It is known that Systemic Rheumatic Diseases (SRDs) are associated with accelerated atherosclerosis. Chronic inflammation results in development of atherosclerotic plaque and endothelial dysfunction. Pentraxin 3 may be a
useful tool to identify SRDs in patients at higher risk of cardiovascular diseases (Atzeni et al., 2010; Hollan et al., 2010). Also, in a study with 130 patients with Systemic Lupus Erythematosus (SLE), anti-PTX3 antibodies were found to be significantly prevalent in patients with SLE. It was also reported that, in these patients, PTX3 might provide protection from renal involvement (Bassi et al., 2010). Deniz et al. (2013) also found that, as a result of inflammation, serum PTX3 levels might be elevated in patients with ankylosing spondilitis (Deniz et al., 2013). It was reported that, in patients with Rheumatoid Arthritis, PTX3 could be a novel biomarker for vascular involvement (Klimek et al., 2014; Hollan et al., 2013; Luchetti et al., 2000).

CONCLUSION

Pentraxin 3 is a long pentraxin, consisting of a C-terminal pentraxin module coupled with an unrelated N-terminal domain (Breviario et al., 1992). PTX3 is structurally related but distinct from the classic short pentraxins, C-reactive protein and serum amyloid P component, differing in gene organization and localization, ligand recognition, producing cells, and inducing signals. PTX3 is expressed in macrophages, dendritic cells, neutrophils, and vascular endothelial cells (ECs), but not in the liver, in response to primary proinflammatory signals such as bacterial products, interleukin–1, and tumor necrosis factor-alpha, but not interleukin–6 (Daida, 2011). Pentraxin 3 is unspecific as a marker with proven associations not only with severe infections but also with other conditions, e.g. states of cardiovascular disease. High PTX3 level has been observed to correlate with unfavourable outcome in several acute conditions. Serial measurements of PTX3 have been especially useful, as persisting high level of PTX3 is associated with poor prognosis (Juutilainen et al., 2011). After reviewing the literature, we concluded that PTX3 is a useful marker for patients with CAD, ALI and nephrologic diseases. It is also a good predictor of mortality in patients with CVD. However, its usefulness in hematological malignancies, neutropenic fever and sepsis is controversial. Additionally, increased level of PTX3 in a broad spectrum of diseases decreases its specificity and diagnostic value. Further investigations are needed to reveal its exact utility in diseases with inflammatory origin.

Conflict of interests

None to declare

REFERENCES


