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Review

# Interleukin-18 bioactivity: a novel target for immunopharmacological anti-inflammatory intervention

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**Abstract**

Interleukin-18 is a member of the interleukin-1 family of cytokines with pro-inflammatory and tumor-suppressive properties. Its ability to potently enhance the production of interferon-γ indicates in particular the crucial function of interleukin-18 as an immunomodulatory molecule. In fact, high levels of interleukin-18 are detected in human diseases associated with immunoactivation including viral or bacterial infections and chronic inflammation. Animal models suggest suppression of interleukin-18 bioactivity as a novel therapeutic concept specifically for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis. Here we introduce into the biology of interleukin-18 and review immunopharmacological strategies that aim at reducing interleukin-18 bioactivity in human disease.


*Keywords:* Interleukin-18; Interleukin-1β; Interleukin-18 binding protein; Caspase-1; Inflammation

**Contents**



## 1. Introduction

Interleukin-18, formerly introduced as interferon-γ-inducing factor, is a cytokine that shares structural and functional properties with interleukin-1 (Bazan et al., 1996; Okamura et al., 1995; Dinarello, 1996; Gracie et al., 2003; Dinarello and Fantuzzi, 2003). Accordingly, interleukin-18 displays pro-inflammatory properties which are at least in part mediated by activation of the transcription factors nuclear factor-κB and activator protein-1 (Matsumoto et al., 1997; Barbulescu et al., 1998; Sugimoto et al., 2003). By its ability to induce production of tumor necrosis factor-α and interleukin-1β in mononuclear cells (Puren et al., 1998), interleukin-18 is able to initiate a cytokine cascade with concomitant expression of pro-inflammatory markers such as chemo-

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Table 1

| Upregulation of IL-18 in human inflammatory and autoimmune diseases | |
|---|---|
| Rheumatoid Arthritis | Yamamura et al. (2001) |
| Still's Disease | Kawashima et al. (2001) |
| Systemic Lupus Erythematosus | Wong et al. (2000) |
| Psoriasis | Koizumi et al. (2001) |
| Crohn's Disease | Pages et al. (2001) |
| Chronic Liver Disease | Ludwiczek et al. (2002) |
| Acute Pankreatitis | Rau et al. (2001) |
| Allergic Rhinitis | Verhaeghe et al. (2002) |
| Type I Diabetes | Nicoletti et al. (2001a) |
| Atherosclerosis | Mallat et al. (2001a) |
| Multiple Sclerosis | Nicoletti et al. (2001b) |
| Sarcoidosis | Shigehara et al. (2001) |
| Nephrotic Syndrome | Matsumoto and Kanmatsuse (2001) |
| Chronic Heart Failure | Yndestad et al. (2003) |
| Myasthenia Gravis | Jander and Stoll (2002) |
| Sepsis | Grobmyer et al. (2000) J. Clin. Immunol. |

kines (Puren et al., 1998), nitric oxide (Zhang et al., 1997), adhesion molecules (Kohka et al., 1998), and matrix metalloproteinase-9 (Nold et al., 2003a,b). Certainly the most prominent function of interleukin-18 is its capacity to act as a potent costimulus for interferon-γ production by T cells and natural killer cells. Accordingly, interleukin-18 is regarded to be a pivotal mediator of Th1 cytokine responses. Although interleukin-1 is able to enhance interferon-γ generation too, direct comparison revealed that interleukin-18 is far more potent in this regard (Nakamura et al., 1989; Okamura et al., 1995; Hunter et al., 1997). However, recent data imply that interleukin-18, in the absence of interleukin-12, may also facilitate the development of Th2 responses (Nakanishi et al., 2001). In contrast to interleukin-1, interleukin-18 is not able to induce a febrile response in mice (Gatti et al., 2002). A further striking difference between interleukin-18 and other pro-inflammatory cytokines such as interleukin-1β or tumor necrosis factor-α is the fact that the former cytokine is constitutively expressed in a wide array of human cell types, among them colon carcinoma cells (Takeuchi et al., 1999), peripheral blood mononuclear cells (Puren et al., 1999), and keratinocytes (Kämpfer et al., 2000). This characteristic together with its ability to induce expression of tumor necrosis factor-α implies that interleukin-18 is located at a rather proximal position in the inflammatory cytokine cascade, a premise which recommends interleukin-18 as a prime target for anti-cytokine therapy. This therapeutic concept agrees with overproduction of interleukin-18 in human inflammation (Table 1). Although this does not proof a causative relationship, it is interesting to note that in some of these diseases interleukin-18 clearly correlates with clinical severity, e.g. in Still's disease (Kawashima et al., 2001), psoriasis (Gangemi et al., 2003), and systemic lupus erythematosus (Wong et al., 2000).

Besides its function as a mediator of inflammation, interleukin-18 has tumorsuppressive properties. These are mediated by interferon-γ-dependent and -independent

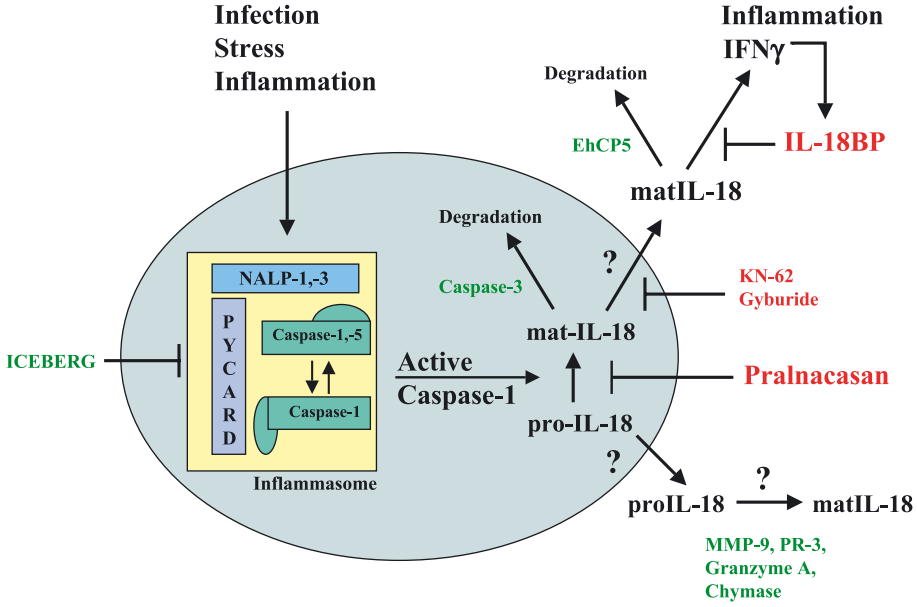


Fig. 1. Pathways that regulate bioactivity of interleukin-18. NALP-1 or NALP-3 and PYCARD are major components of large ($10^6$ Da) protein complexes that have been introduced as NALP-1 or NALP-3 inflammasomes (Tschopp et al., 2003; Agostini et al., 2004). The NALP-3 inflammasome contains a further important adaptor protein termed Cardinal (omitted from this figure). Inflammasome assembly mediates activation of caspase-1 with subsequent processing of pro-interleukin-1β or pro-interleukin-18. Potential sites of immunopharmacological intervention aiming at inhibition of interleukin-18 bioactivity are shown in red (IL, interleukin; IL-18BP, IL-18 binding protein; MMP-9, matrix metalloproteinase-9; NALP, NACHT/LRR/PYD-containing proteins; PYCARD, PYD and Card-containing protein).

mechanisms that include inhibition of angiogenesis and upregulation of Fas-dependent killing (Dao et al., 1996; Osaki et al., 1998; Oshikawa et al., 1999; Cao et al., 1999; Liu et al., 2002). However, the role of interleukin-18 in tumor biology may be more complex. In fact, blockage of interleukin-18 bioactivity resulted in reduced metastasis in a murine melanoma model (Carrascal et al., 2003), an observation that reflects interleukin-18-induced expression of vascular cell adhesion molecule-1 (Vidal-Vanaclocha et al., 2000) and that may also be related to induction of matrix metalloproteinase-9 by this cytokine (Gerdes et al., 2002; Nold et al., 2003a,b). These observations concur with tumor promotion by interleukin-1β in the same melanoma model (Vidal-Vanaclocha et al., 2000). Thus, pro-inflammatory properties of interleukin-18, which basically can promote tumor growth, may be able to overcome its tumorsuppressive functions under certain conditions. Interleukin-18 also is a growth factor for murine melanoma cells (Carrascal et al., 2003). Interestingly, high serum levels of interleukin-18 correlate with poor outcome in patients with multiple myeloma (Alexandrakis et al., 2004) or esophageal carcinoma (Tsuboi et al., 2004) and serum interleukin-18 is elevated in patients with metastatic breast cancer compared to the non-metastatic condition or healthy control subjects (Günel et al., 2002).

Current knowledge on the biology of this cytokine implies that suppression of interleukin-18 bioactivity is a promising novel strategy for the treatment of chronic inflammatory/autoimmune diseases. Given its constitutive expression in many cell types, it can be assumed that interleukin-18 is released rather early in the pro-inflammatory cytokine cascade. Thus, it may be that anti-interleukin-18 strategies show high efficacy when compared to interleukin-1 or tumor necrosis factor-α blockage. In the following sections, pathways that regulate interleukin-18 bioactivity as well as pharmacotherapeutic strategies that aim at blocking interleukin-18 bioactivity are being reviewed (Fig. 1). This provides new facets to previously described initiatives for selective immunotherapy (Pfeilschifter and Mühl, 1999).

## 2. Significance of interleukin-18 in chronic inflammation as detected in interleukin-18 deficient mice

Interleukin-18 deficient mice were generated (Takeda et al., 1998; Wei et al., 1999) and have been evaluated in key models of chronic inflammation in recent years. The results of these studies are encouraging and underscore the potential of anti-interleukin-18 strategies for the treatment of inflammatory diseases. Specifically, in collagen-induced arthritis incidence and severity of disease was significantly reduced in interleukin-$18^{-/-}$ mice compared to their heterozygote or wildtype counterparts (Wei et al., 2001). Similar results have been obtained in experimental autoimmune encephalomyelitis, a murine model for multiple sclerosis (Shi et al., 2000). In both studies protection has been related to an impaired capability of leukocytes obtained from interleukin-$18^{-/-}$ mice to produce tumor necrosis factor-α and interferon-γ. Lack of interleukin-18 was also protective in 2,4,6-trinitrobenzene sulfonic acid-induced colitis (Kanai et al., 2001) and in experimental autoimmune diabetes (Lukic et al., 2003). In addition to these data on chronic inflammation, interleukin-$18^{-/-}$ mice were resistant in models of Fas ligand- or lipopolysaccharide-induced liver injury in *P. acnes* primed mice (Sakao et al., 1999; Tsutsui et al., 1999).

## 3. Processing and secretion of interleukin-18 as a potential target for immunopharmacological intervention

Pro-interleukin-18, in similarity to pro-interleukin-1β, is converted into biological active mature interleukin-18 by action of the intracellular protease caspase-1 which is also known as interleukin-1β converting enzyme (Fantuzzi and Dinarello, 1999; Creagh et al., 2003). Activation of Caspase-1 appears to be mediated by large protein complexes defined as inflammasomes. At least two inflammasomes can be distinguished, the NACHT/LRR/PYD-containing protein (NALP)-1 and the NALP-3 inflammasome. It has been proposed that at the inflammasome inactive pro-caspase-1 is converted into the active protease by interaction with another caspase-1 molecule (NALP-3 inflammasome) or with the protease caspase-5 (NALP-1 inflammasome) (Tschopp et al., 2003; Agostini et al., 2004). Interference with the assembly of the inflammasome would suppress caspase-1 activation. This may be achieved by the action of regulatory proteins such as ICEBERG, which has been shown to inhibit processing of pro-interleukin-1β via modulation of caspase-1 activation. Since ICEBERG is induced by pro-inflammatory cytokines, a negative feedback loop appears to operate through this protein that may control caspase-1 activity in an inflamed microenvironment (Humke et al., 2000).

Inhibition of caspase-1 appears to be a promising pharmacotherapeutic strategy since supression of both, interleukin-1β and interleukin-18 bioactivity, should be achieved by this approach. Actually, caspase-1 deficient mice or mice treated with the caspase-1 inhibitor pralnacasan show protection in the model of dextran sulphate sodium-induced colitis (Siegmund et al., 2001; Loher et al., 2004). Caspase-1 inhibition was also protective in collagen-induced arthritis (Ku et al., 1996; Randle et al., 2001). The orally available agent pralnacasan has been the first caspase-1 inhibitor to undergo clinical testing for its therapeutic potential in chronic inflammation, specifically in rheumatoid arthritis patients. In that phase IIa clinical trial pralnacasan was well tolerated and demonstrated anti-inflammatory properties by significantly reducing markers of inflammation such as the erythrocyte sedimentation rate,

C-reactive protein, and serum amyloid A (Siegmund and Zeitz, 2003). However, effects of pralnacasan on clinical symptoms appear moderate, particularly when compared with effects that can be achieved by tumor necrosis factor-α blocking strategies (Garrison and McDonnell, 1999). An explanation may be the phenomenon of caspase-1-independent processing of pro-interleukin-1β and pro-interleukin-18. Close structural similarities and cleavage of both molecules by intracellular caspase-1 suggest that pro-interleukin-1β and pro-interleukin-18 might be proteolytically activated by a very similar set of extracellular proteases. The existence of such alternative caspase-1-independent pathways that mediate processing of interleukin-1β and interleukin-18 has been demonstrated for the murine and the human system. For example, generation of mature interleukin-1β can be observed in a model of local inflammation in caspase-1 deficient mice (Fantuzzi et al., 1997). Furthermore, macrophages from *P. acnes*-primed mice release mature interleukin-18 in response to stimulation by Fas ligand. Again, usage of knockout mice identified this process as caspase-1-independent (Tsutsui et al., 1999). In another study, release of biological active mature interleukin-18 from human oral epithelial cells was detected after exposure to lipopolysaccharide/interferon-γ plus proteinase-3. Interestingly, these cells lack expression of caspase-1. Accordingly, generation of mature interleukin-18 was not suppressed under the influence of the caspase-1 inhibitor YVAD-CHO (Tyr-Val-Ala-Asp-aldehyde) (Sugawara et al., 2001). These reports illustrate that under certain conditions proteolytic mechanisms are in place that ensure caspase-1-independent maturation of pro-interleukin-1β and pro-interleukin-18. These mechanisms may obviously confine the potential of caspase-1 inhibition in anti-inflammatory pharmacotherapy. Candidate extracellular proteases that may be able to take over for caspase-1 are mast cell chymase (Mizutani et al., 1991), matrix metalloproteinases (Schönbeck et al., 1998), granzyme A (Irmler et al., 1995), and proteinase-3 (Fantuzzi and Dinarello, 1999). Additional studies are needed to further characterize the role of caspase-1-independent processing of pro-interleukin-1β and pro-interleukin-18 in human inflammation.

Both, pro-interleukin-1β and pro-interleukin-18, are proteins that lack a signal peptide which usually directs a protein to the secretory apparatus of the cell. Molecular mechanisms regulating the release of these two leaderless proteins are assumed to be very similar but are still incompletely understood. In particular release of interleukin-18 from cells, including monocytes/macrophages, is a rather inefficient process. Actually, induction of interleukin-18 secretion by lipopolysaccharide-stimulated peripheral blood mononuclear cells was not observed, neither in the form of pro-interleukin-18 nor as mature interleukin-18. Instead, a constitutive release of pro-interleukin-18 from these cells was apparent and this process was not affected by the presence of lipopolysaccharide. In contrast, lipopolysaccharide-induced interleukin-1β liberation was evident under these conditions (Puren et al., 1999).

Extracellular ATP-mediated activation through the purine $P_{2x7}$ receptor is able to mediate cellular responses that trigger efficient release of interleukin-18 from human whole blood, monocytes, peripheral blood mononuclear cells, and microglial cells (Perregaux et al., 2000; Mehta et al., 2001; Mühl et al., 2003; Rampe et al., 2004). In fact, ATP is the only known endogenous stimulus which is able to initiate rapid and ample processing and liberation of interleukin-1β and interleukin-18. This process is associated with a cellular $K^+$ efflux and activation of caspase-1 (Kahlenberg and Dubyak, 2004). Secretion itself appears to be independent on caspase-1 activity since augmented liberation of pro-interleukin-18 is evident under the influence of the caspase-1 inhibitor YVAD-cmk (Mehta et al., 2001). Prolonged activation of the purine $P_{2X7}$ receptor eventually leads to cell death that can be detected after several hours of stimulation (MacKenzie et al., 2001; Di Virgilio et al., 1998). However, release of interleukin-18 and cell death in response to purine $P_{2X7}$ receptor activation appear to be independent processes. In fact, it has been shown that purine $P_{2X7}$ receptor activation induces a rapid (within 2 min) shedding of microvesicles from lipopolysaccharide-primed human monocytes. These microvesicles contain mature interleukin-1β and, taken into account the similarities between interleukin-1β and interleukin-18, most likely also mature interleukin-18. With a time lag of 2–10 min, interleukin-1β is then released from these microvesicles and can be detected in the microvesicle-free supernatant. This whole process of purine $P_{2X7}$ receptor-mediated rapid liberation of interleukin-1β is not associated with a loss of cell viability (MacKenzie et al., 2001). Moreover, purine $P_{2X7}$ receptor-mediated release of interleukin-1β from lipopolysaccharide-primed murine Schwann cells is not accompanied by cell death (Colomar et al., 2003). Expression of purine $P_{2x7}$ receptor is upregulated by pro-inflammatory stimuli like lipopolysaccharide/interferon-γ (Humphreys and Dubyak, 1996). The significance of extracellular ATP signaling via the purine $P_{2x7}$ receptor in an inflammatory setting is furthermore highlighted by the observation that purine $P_{2x7}$ receptor knockout mice show greatly reduced lipopolysaccharide-mediated inflammatory responses in a model of experimental arthritis (Labasi et al., 2002). We could recently demonstrate that release of interleukin-18 from lipopolysaccharide/ATP-stimulated human peripheral blood mononuclear cells is efficiently inhibited by the purine $P_{2X7}$ receptor antagonist KN-62. In that study, release of interleukin-18 was also suppressed by coincubation with the sulfonylurea glyburide (Mühl et al., 2003). Glyburide is a potent inhibitor of the type 1 ATP binding cassette translocator, the activity of which has been related to release of interleukin-1β under the influence of lipopolysaccharide/

ATP (Hamon et al., 1997). Altogether, these reports suggest that purine $P_{2X7}$ receptor antagonism or inhibition of the type 1 ATP binding cassette translocator may represent promising future strategies that target interleukin-1β and interleukin-18 in human inflammation.

Post-translational control of interleukin-18 bioactivity is also achieved by proteolytical degradation. Examples of such inhibitory pathways are caspase-3 (Akita et al., 1997) and the amebic protease EhCP5 (Que et al., 2003). Both proteases generate biological inactive interleukin-18 fragments. Therefore, pharmacological intervention based on protease inhibition needs to take into account this additional level of complexity.

## 4. Neutralization of interleukin-18 bioactivity by interleukin-18 binding protein

Extracellular interleukin-18 bioactivity is controlled by the interleukin-18 binding protein, a secreted decoy receptor that binds to and thereby inactivates this cytokine (Aizawa et al., 1999; Novick et al., 1999). In comparison to the interleukin-1 system, interleukin-18 binding protein can be regarded as a functional homologue of the type II receptor for interleukin-1. Like interleukin-18, interleukin-18 binding protein is a constitutively expressed gene. Consequently, interleukin-18 binding protein and its counterpart interleukin-18 are readily detectable in sera of healthy humans (Novick et al., 2001). Therefore, to a certain degree, constitutive production of interleukin-18 binding protein appears to establish a protective buffer for interleukin-18 which may be released by dying cells even under non-pathological conditions. Although being a constitutively expressed gene, interleukin-18 binding protein is also inducible. In fact, elevated levels of interleukin-18 binding protein have been observed in human inflammation, e.g. sepsis (Novick et al., 2001), Crohn's disease (Corbaz et al., 2002), and psoriasis (Koizumi et al., 2001). Chief activator of interleukin-18 binding protein production appears to be interferon-γ. Interleukin-18 binding protein induction by interferon-γ likely operates in all cell types that express functional receptors for interferon-γ has been demonstrated in vivo in mice, and implements a negative feedback loop that may be essential for controlling excessive interleukin-18 bioactivity in pathophysiology (Mühl et al., 2000; Paulukat et al., 2001; Veenstra et al., 2002; Hurgin et al., 2002; Möller et al., 2003; Mühl and Pfeilschifter, 2003). In accord with these observations, it has been shown in vivo that lipopolysaccharide mediates hepatic expression of interleukin-18 binding protein in rats and likewise in *P. acnes*-primed mice (Dong et al., 2002; Wheeler et al., 2003).

Human interleukin-18 binding protein is a naturally occurring protein that obviously should not mediate side effects related to antibody therapy. In comparison to other naturally occurring cytokine antagonists (e.g. interleukin-1 receptor antagonist), interleukin-18 binding protein is highly active in neutralizing its natural counterpart. Actually, at a molar excess of only two, interleukin-18 binding protein is able to neutralize interleukin-18 bioactivity at least by 95% (Kim et al., 2000). These properties make interleukin-18 binding protein an attractive candidate for immunopharmacological therapy aiming at suppression of interleukin-18 bioactivity in inflammation. In fact interleukin-18 binding protein is protective in murine models of inflammatory/autoimmune diseases. Application of interleukin-18 binding protein significantly decreased clinical severity in collagen-induced arthritis (Plater-Zyberk et al., 2001; Banda et al., 2003). Inhibition of disease was associated with reduction of local expression of interleukin-1β, tumor necrosis factor-α, and interferon-γ in the affected joints. In contrast, expression of interleukin-1 receptor antagonist was not modulated by interleukin-18 binding protein. Moreover, injection of interleukin-18 binding protein reduced production of immunoglobulin G1 and immunoglobulin G2a and impaired T cell proliferation ex vivo (Banda et al., 2003). Protection by interleukin-18 binding protein was likewise observed in 2,4,6-trinitrobenzene sulfonic acid- or dextran sulphate sodium-induced colitis in mice (Ten Hove et al., 2001; Sivakumar et al., 2002). Again, treatment with interleukin-18 binding protein was associated with a reduction in local pro-inflammatory cytokine production. Notably, interleukin-18 binding protein gene therapy was successfully applied in collagen-induced arthritis (Smeets et al., 2003) and in a model of murine atherosclerosis (Mallat et al., 2001b). These reports illustrate that interleukin-18 binding protein is active in suppressing chronic inflammation in mice. In accord with these reports on murine models, interleukin-18 binding protein also demonstrates anti-inflammatory properties in human whole blood cultures (Stuyt et al., 2001; Nold et al., 2003b). Notably, in a subset of experiments lower concentrations of interleukin-18 binding protein were more effective than higher concentrations in reducing interferon-γ production by human whole blood cultures (Nold et al., 2003b). This observation appears to reflect the properties of interleukin-18 binding protein as a therapeutic agent in collagen-induced arthritis in mice (Banda et al., 2003). The encouraging pre-clinical data on interleukin-18 binding protein in murine models of chronic inflammation form the basis of current clinical trials that evaluate the therapeutic potential of interleukin-18 binding protein as a treatment option for patients with psoriasis or rheumatoid arthritis (see [http://www.serono.com/index.jsp]).

## 5. Concluding remarks

Anti-cytokine strategies targeting excessive interleukin-1 or tumor necrosis factor-α bioactivity have been

successfully incorporated in current pharmacotherapy of chronic inflammatory diseases, in particular rheumatoid arthritis and Crohn's disease (Garrison and McDonnell, 1999; Sands, 2000; Cunnane et al., 2001; Gabay, 2002). Generally, these biologicals are well tolerated. However, it must be appreciated that pro-inflammatory cytokines are of key importance in host defense against infection. In fact, an increased risk of opportunistic infections has been associated particularly with neutralization of tumor necrosis factor-α (Cunnane et al., 2003; Dinarello, 2003; Gomez-Reino et al., 2003; Colombel et al., 2004). Similar observations may become apparent during therapeutic suppression of interleukin-18 function. A major obstacle of anti-cytokine therapy are the so-called non-responders who, depending on the study and the biological in use, can make up 28–50% of the respective patient population (Redlich et al., 2003). Identification of these non-responders in an early phase of pharmacotherapy is an important aim of current research. Suppression of interleukin-18 bioactivity may provide an important additional therapeutic approach aiming at the group of patients who failed conventional anti-inflammatory intervention.

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