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Corticosteroid Resistant Pulmonary Fibrosis: Pathophysiology and Management

Doha O. Alghamdi[1*], Hala S. Abdel Kawy[1] and Zoheir A. Damanhouri[1]

[1]Department of Pharmacology, Faculty of Medicine, King Abdul-Aziz University, Jeddah, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Pulmonary fibrosis is a disease of the lower respiratory system. It might be as Idiopathic fibrosis which is obscure reason for disease or might be as an optional impact from different causes, for example, the environmental causes, for example, toxins and smoking, some connective tissue illnesses., infection diseases, for example, tuberculosis (TB) and corona virus, a few medications, for example, bleomycin, methotrexate, and radiation treatment. Glucocorticoid are used for treating inflammatory and immune diseases, like asthma, but interstitial lung disease, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) at some stage, may become resistant to corticosteroid treatment. Glucocorticoids inhibit inflammation by many mechanisms. The oxidative stress leads to significantly decrease in activity and expression of Histone deacetylase 2 (HDAC-2) which causes resistant to the action of glucocorticoid. However, the dissociated glucocorticoids have been developed to decrease side effects, the dissociated glucocorticoid receptor agonists (DIGRAs) are a class of experimental drugs designed to share many of the desirable anti-inflammatory, immunosuppressive, or anticancer properties of classical glucocorticoid drugs with fewer side effects, but it is so difficult to dissociate anti-inflammatory effects from adverse effects. Patients with glucocorticoid resistance must use alternative anti-inflammatory treatments as well as drugs that may reverse the molecular mechanism of glucocorticoid resistant. Objective: This

**Corresponding author: E-mail: dohaalghamdi93@gmail.com;*

paper is to review the corticosteroid resistant pulmonary fibrosis and how overcome this resistance.
The data was collected from December 2020 to September 2021.

Keywords: Corticosteroid; resistance; pulmonary fibrosis; pathophysiology; management.

1. INTRODUCTION

The interstitial lung diseases (ILDs) are different classification of lung diseases that are characterized by prolonged inflammation and progressive fibrosis of the pulmonary interstitium [1]. The risk factors of pulmonary fibrosis such as; smoking, gastroesophageal reflux, commonly prescribed drugs such as anti-epileptics, beta blocker (βB), antibiotics, and nonsteroidal anti-inflammatory drugs [NSAIDs], diabetes mellitus, environmental exposures, infectious agents and genetic factors [2].

Objectives: This paper is to review the corticosteroid resistant pulmonary fibrosis and how overcome this resistance.

Methods: Review article

2. PATHOPHYSIOLOGY OF PULMONARY FIBROSIS

In brief, the alveolar epithelial cell injury is a key process in the pathogenesis of pulmonary fibrosis followed by release the profibrotic cytokines such as chemokines, proteases, transforming growth factor-beta [TGF-β] (Wolters et al., 2014).

The injury of alveolar epithelial cell and apoptosis is followed by type II alveolar cell injury and abnormal lung function, activation of pathways of coagulation, and loss wound healing mechanisms that progressively interrupt lung matrix when fibroblasts are stimulated as epithelial-to-mesenchymal transition (EMT) of alveolar epithelial cells happens, which leading to activation and accumulation of myofibroblasts [90-94]. Those results, unable the tissue remodeling to regenerate the normal barriers of epithelial or suppress the normal behavior and expansion of myofibroblasts and the entry of circulating myofibroblast [3].

Type II alveolar cell dysfunction leading to inability of the lung to wound healing. Additionally, the dysfunction of Type II alveolar epithelial cell as a factor which is linked with impaired regeneration of damaged alveolar epithelium, which leads to abnormal tissue remodeling and progressive pulmonary fibrosis and prevents repair of injury. Commonly, in pulmonary fibrosis resolution of inflammatory and mesenchymal cells through apoptosis and phagocytosis is dysregulated. This results in the destroyed of the normal lung structure and dysfunction (Wolters et al., 2014).

General pathogenesis of pulmonary fibrosis: There three stages of pulmonary fibrosis, the first sage is injury, the second stage is inflammation, and the third stage is repair.

2.1 Firstly, Injury Stage

The damage of cells is an acute injury leading to the stimulation of inflammatory mediators and initiation the pathway of fibrinogenesis and coagulation, the platelet and fibrin-rich clot reach to the damaged vessel with a platelet [4].

Furthermore, thrombin found within the lung and the space between alveolar of many pulmonary fibrotic cases. Fibroblast is stimulated by thrombin, rising proliferation, and encouraging fibroblast differentiation into collagen-producing myofibroblasts [5]. Damage to the airway epithelium, particularly, alveolar pneumocytes can evoke a similar fibrinogenesis pathway and cause edema and acute inflammation areas. Rapidly dilated vessels during clot formation and increased permeability, leading to migration of leukocytes to the injured site [4].

Matrix metalloproteinase (MMP) is a set of Zn-dependent proteinases stimulated by proteolytic deletion of their amino terminal, and their actions are controlled by regulation of transcription, regulation of proenzyme, specific matrix metalloproteinases inhibitors and matrix metalloproteinases tissue inhibitors [4]. MMP-2 and MMP-9 are (gelatinase A, Type N collagenase) and (Gelatinase B, Type IV collagenase), respectively. MMP-2 and MMP-9 have ability to destroy the type IV of collagen, the MMP-2 and MMP-9 are the main compositions of membrane [95-101]. Studies showed that the

activity of MMP-2 and MMP-9 is organized in pulmonary fibrosis [6].

The balance between MMPs and the several inhibitory mechanisms can control inflammation and detect the clear sum of collagen deposited during the response healing [4].

2.2 Secondly, Inflammation Stage

Once tissue is damaged, chemical gradients and inflammatory cells are released. At the site of infection as an acute injury (neutrophils, eosinophils, lymphocytes, and macrophages) are existed with eliminated the necrosis area by macrophages [4].

The primary inflammation that is reduced at the later phases of disease may encourage healing of wound and may part of fibrosis. E.g., the early inflammatory response such as (eosinophils, neutrophils, lymphocytes, and macrophages) which are providing cytokines and chemokines to stimulate the local TGFβ and IL-13 [29-37]. As a following of the initial inflammatory response, is late stage of inflammatory cells may support in phagocytosis, support in phagocytosis clear cell debris, and control excessive cellular proliferation, which these may leading to normal healing. In end phase of inflammation may play important role in anti-fibrotic for repair injury and response. In addition, the interleukin-10 production organizes T cells, inhibiting limited site chemokine production and TGFβ, may avoid extreme fibroblast stimulation [4].

The Th1 response includes increased INF-c expression and interleukin (IL-2, IL-12 and IL-18), all of which support cell-mediated immunity and in general encourage tissue repair. In difference, the Th2 cytokines include (IL-4, IL-5, IL-10 and IL-13) are more involved with antibody-mediated immunity, and tend to stimulate fibroblast activation, development of matrix and scar formation [4].

Most of cytokines stimulated in immune cells to damage site including the cell adhesion molecules. Additionally, many cytokines are supporting the healing of wounds and response of fibrosis. The pro-inflammatory cytokines are more found in fibrosis such as (IL-1α, IL-1β, TNFα, TGFβ, and platelet-derived growth factors (PDGF), while many cytokines in different pulmonary fibrotic cases such as IL-4, IL-13, and TGF-β take a consider [3].

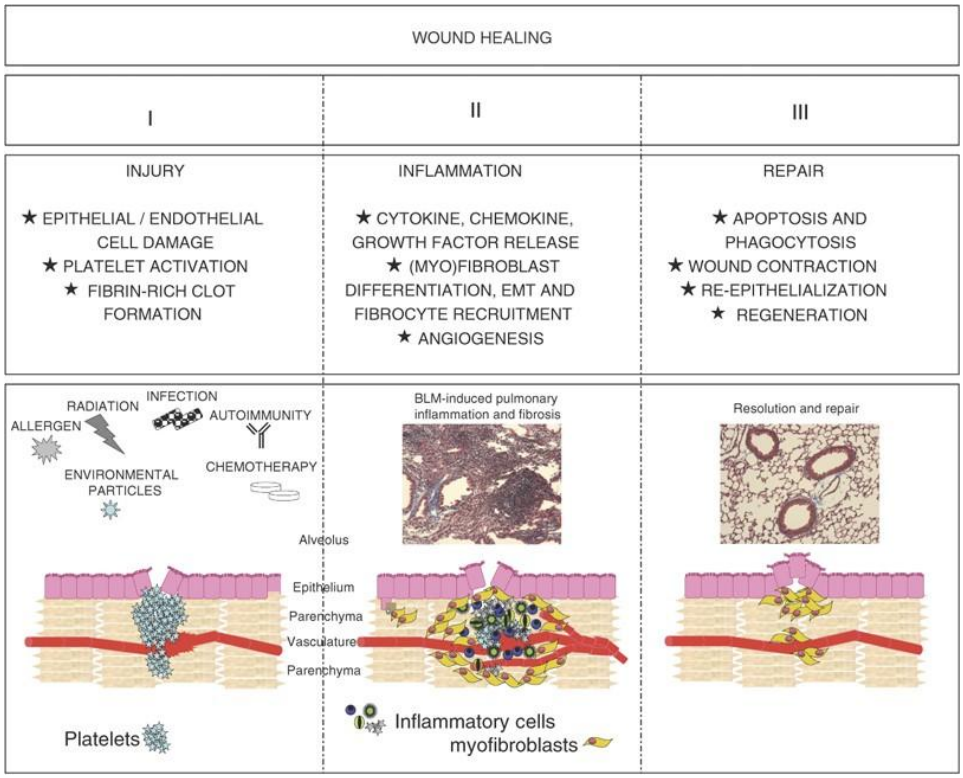

Fig. 1. The three stages of pulmonary fibrosis
Stages of pulmonary fibrosis [4]

In particularly, IL -4, is a cytokine type 2, it has also known as a pro-fibrotic cytokine, and it is increased in pulmonary fibrosis. The receptors of interleukin-4 are existing on lung fibroblasts with IL-4 signaling rising the matrix proteins of extra cellular and deposition of collagen. Surprisingly, it considers in many studies also increase the level of IL 4 is marker in fibrosis above to TGF-β1 at inducing synthesis of collagen from fibroblasts [4].

Additionally, IL-4 can stimulate the alternative activation of Macrophage by indirect action. In generally, macrophage is associated with pulmonary fibrosis. Furthermore, the TGF-β, PDGF modulate polyamine and proline biosynthesis, cell growth, and collagen formation are produced by macrophage [102-111]. Also, IL-4 has ability to encourage the T cells differentiation to Th2 cells, providing source of a lot of cytokines type-2 in axis of inflammation such as (L-5, IL-9, IL-13, and IL-21). The cytokines of Th2 has effective role in the healing of wound and profibrotic response such as in the Table 1 [4].

The TGFβ is the most profibrotic cytokines. It derived from most cell derived from the bone marrow. Once active, TGFβ is stimulating fibroblast proliferation and the synthesis of extracellular matrix proteins, recruiting inflammatory cells through monocyte chemoattractant protein-1 (MCP-1) (CCL2) and inhibiting T-cell responses with contribute to healing of wound and fibrosis [4].

In chronic injury, the cells of endothelia go on a process of formation of vessel with grow up of new capillary branches from existing vessel of blood (angiogenesis) which are enter to fibrotic tissue and regenerative tissue. The VEGF and FGF, TGFβ, PDGF, Angiopoietin1 and a vast array of cytokines are the angiogenic factors which can be controlled the angiogenesis factor [4].

An imbalance in production of chemokine with uncontrolled cellular recruitment which leads to excessive of pro-fibrotic IL-13 or TGF-β, with highly production of myofibroblasts, leading a pathological fibrosis [7].

2.3 Thirdly, Stage of Repair

Repair is a blend of recovery and scarring development in tissue repair relies upon the capacity of the tissue to recover and the degree of the injury. The formation scar is a process that happens when the extracellular matrix (ECM) is harmed by extreme injury. Myofibroblast-derived collagens and α-SMA form the temporary extracellular matrix, with macrophage, platelet, and fibroblast-derived fibronectin forming a fibrin scaffold [4].

In addition to fibronectin, the temporary extracellular matrix contains of glycoproteins e.g. (PDGF), glycosaminoglycans e.g. (Hyaluronic acid), proteoglycans, and elastin [8].

The fibroblast stimulated by Growth factor and TGFβ migrate along the extracellular matrix network and repair the wound. The transformation of fibroblast to myofibroblast differentiation is makes stress fibers and the neo-expression of α-SMA, which are enhance activity within myofibroblasts [38-52]. The connection of myofibroblasts to the extracellular matrix at specific sites called the “fibro nexus” or “super mature focal adhesions” pull the wound together, decreasing the size of the wound during this phase. At the end there is a variation in control the balance between MMP and TIMPs and the balance between collagen and collagenases, shifting from pro-synthesis and increased collagen deposition, towards a controlled balance, with no net rise in collagen [4].

However, the usual response of tissue to lesion has a sequence for successful resolution, repair of tissue and regain normal lung function such as the elimination of inflammatory cells and particularly α-SMA+ myofibroblasts is important to dismiss deposition of collagen. But the Failure to control the process of healing which is caused remodeling of tissue and abnormal functional tissue with formation of scar tissue [8].

Finally, the level of inflammation, angiogenesis, and the amount of deposition of extracellular matrix all encourage to deposition of collagen and develops of scar [4].

L-Hydroxyproline is a non-proteinogenic, insignificant amino acid that is found in collagen and other extracellular animal proteins. L-Hydroxyproline is one of 18 kinds of amino acids found in mammalian collagens, is a significant constituent of collagen, and exists primarily in collagen (elastin contains around 1%). L-Hydroxyproline likewise assumes significant part in the synthesis of collagen and stability [112-119]. Thus, collagen is a specific amino acid and a significant marker that can be utilized to straightforwardly quantify the collagen content in IPF tissues. As of

Table 1. The function of ILs in pathophysiology of pulmonary fibrosis [4]

Interleukins	Description
Interleukin (5)	Moves, matures, and recruits eosinophils, with IL-4 stimulation the production of TGF-β from eosinophils. It can also increase the production of IL-13 in fibrosis.
Interleukin (9)	It has ability to selective activation of mast cells, with increase the activity of TGFβ and promote the pulmonary fibrosis. Mast cells has ability to encourage the proliferation of fibroblast, synthesis of collagen, and production of MMP and involved in fibrosis
Interleukin (21)	It has ability to increase the Th2 pulmonary responses
Interleukin (13)	It is associated fibrosis by regulation receptor expression of IL-4/IL-13. It is not decreasing the level during treatment by steroid. It has a different receptor subunit, it has ability to motivate activator of plasminogen and MMP-9, improving the release of active TGFβand followed by fibrosis.

late, collagen has been drawing in expanding consideration as a significant biomarker of pulmonary fibrosis [9].

2.4 Oxidative Stress

The lungs are generally vulnerable to oxidative stress due to of the highest degrees of oxygen inside the lung. The pressure of oxygen of breathed in air and the strain of oxygen of alveolar air are (150 mm Hg) and (100 mm Hg) individually, while venous blood oxygen pressures getting back from a few organs around (~ 45 mm Hg - ~ 1 mm Hg) [10]. Oxidative stress plays a significant part in molecular mechanism underlying fibrosis in a different of organs, including the lungs [11]. Reactive oxygen species (ROS) assume significant part in specific fibrotic process like macrophage polarization and immuno-senescence, alveolar epithelial cell apoptosis and senescence, myofibroblast differentiation and senescence, and alterations in the acellular extracellular matrix (Otoupalova et al., 2011).

2.5 Role of Integrins in Lung Fibrosis

Integrins are a big family of transmembrane glycoprotein receptors initially known as mediators of cell adhesion and tissue integrity. Integrins act mainly as signaling proteins, transmitting a mixture of signals involved in cell growth, division, survival, differentiation, and apoptosis. Integrins do not contain any catalytic activity and do not independently initiate signaling cascades, but instead serve as scaffolds for the assembly of signaling complexes [120-125]. Integrins are composed of a single α and α single β-subunit. In mammals, there are 18 human α -subunits and eight β-subunits that can form a total of 24 integrin heterodimers [12].

Several specific integrins have been shown to play a role in pulmonary fibrosis in animal models or to have an important biological role that might contribute to pulmonary fibrosis. One such role involves their interaction with latent complexes of TGF-b [12]. Interestingly, the expression of b3- and b6-integrins is a key protein of alveolar repair and has important rule in wound healing but these integrins resistance to corticosteroid therapy [13].

2.6 Treatment of Pulmonary Fibrosis

2.6.1 Corticosteroids

Corticosteroids are used either alone or in combination with immunosuppressive agents in idiopathic pulmonary fibrosis. The combination of prednisone, azathioprine, and N-acetylcysteine: immune suppression was considered important in the treatment of pulmonary fibrosis [53-59]. It was thought that a two-drug regimen including glucocorticoids in addition to either azathioprine or cyclophosphamide may be superior to glucocorticoids alone. Given some early studies in favor of N-acetylcysteine, clinicians and researchers have examined the potential benefit of this three-drug regimen for pulmonary fibrosis. But this recommendation places a high value on these potential adverse effects of intervention [14].

Likewise, corticosteroids are suggested for the treatment of numerous patients with AE-IPF by the latest worldwide IPF treatment rules. Complicating this proposal is proof from clinical trial exhibiting that corticosteroid, in mix with

immunomodulatory treatment, cause harm in constant IPF. Pervious study found that no evidence that corticosteroid use improves outcomes in IPF patients admitted to the hospital with acute exacerbation [14].

Also, there have been not enough randomized controlled trials to evaluate the efficacy of corticosteroid as monotherapy in pulmonary fibrosis. Furthermore, the long term of corticosteroids use has been shown to be linked with a major number of comorbidities. Interestingly many of cohort studies have found no benefit of treatment with corticosteroids. Also, the corticosteroid is not recommended used as monotherapy [15].

2.6.2 Mechanisms of resistance of glucocorticoid

Glucocorticoids stimulate and inhibit many pro- and anti-inflammatory genes, as well as having post-transcription. Glucocorticoids inhibit the multiple inflammatory genes that are stimulated in chronic inflammatory diseases, such as asthma, by reversing histone acetylation of activated inflammatory genes through binding of liganded glucocorticoid receptors (GR) to coactivator molecules and recruitment of histone deacetylase-2 (HDAC2) to the stimulated transcription complex. At higher concentrations of glucocorticoids GR homodimers interact with sites of DNA recognition to stimulate transcription through raised histone acetylation of anti-inflammatory genes and transcription of many genes linked to glucocorticoid adverse effects [16].

But many cases of inflammatory disease are resistance to steroid medications such as pulmonary fibrosis induced by bleomycin, chronic obstruction pulmonary disease (COPD) and cystic fibrosis increased glucocorticoid resistance is found in patients with inflammatory lung diseases. There are numerous molecular mechanism of corticosteroid resistances such as genetic factors may determine glucocorticoid responsiveness, several abnormalities in function of GR have been described in fibroblasts from patients with FGR [16].

Many single nuclear polymorphisms of glucocorticoid receptor have been linked to altered cellular responses to glucocorticoids and a polymorphism of GRb (GR-9b) is linked with a decreased glucocorticoid trans-repression response. These polymorphisms have yet to be correlated with glucocorticoid resistance in inflammatory diseases [16].

Glucocorticoid receptor modification in numerous ways to reduce their efficacy of nuclear translocation and trans-activation. Phosphorylation may occur because of stimulation of p38 mitogen-activated protein kinase (MAPK), which may be stimulated by the cytokines interleukin (IL)-2 + IL-4 or IL-13, or by macrophage migration inhibitory factor (MIF), of c-Jun N-terminal kinase (JNK) activated by proinflammatory cytokines or of extracellular signal-regulated kinase (ERK) stimulated by microbial superantigens. Additionally, the inflammatory diseases are raised inducible NO synthase (iNOS) expression which generates huge amounts of NO that could increase glucocorticoid resistance. Also, increase the expression of glucocorticoid receptor beta (GRb) is caused by proinflammatory cytokines has been found in glucocorticoid-resistant patients of several diseases [16].

In addition, the excessive stimulation of AP-1 has been identified as a mechanism of glucocorticoid resistance because the AP-1 binds GR then prevents its interaction with GRE and other transcription factors. AP-1 is a heterodimer of Fos and Jun proteins and may be stimulated by TNF-a (pro-inflammatory cytokines), acting within the pathway of JNK. This explains why the raised inflammation reported in severe inflammatory disease results in secondary glucocorticoid-resistance. In high c-Jun in de-polymerization of the cytoskeleton, which may also decrease the activity of GR trans-activating [16].

Cofilin-1 is an actin binding protein that depolymerases the cytoskeleton and in gene studies has been found as displaying raised expression in T-cells from glucocorticoid-resistant compared to sensitive disease. Thus, the overexpression of cofilin-1 results in glucocorticoid resistance in T-cells [16].

The other molecular mechanism of glucocorticoid resistance is abnormal of histone acetylation. Histone acetylation plays an important role in the control of inflammatory genes and the mechanism of action of glucocorticoids. HDAC2 is markedly reduced in activity and expression because of oxidative/nitrative stress so that inflammation becomes resistant to the anti-inflammatory actions of glucocorticoids. The oxidative stress also stimulates phosphoinositide-3-kinase (PI3K)- delta, which

causes to phosphorylation and inactivation of HDAC2. So, the oxidative stress has an important mechanism of glucocorticoid resistance and is increased in most severe and glucocorticoid-resistant inflammatory diseases [16].

Moreover, reduced regulatory T cells which leads to reduce response to glucocorticoid, because IL-10 is an important anti-inflammatory and immunoregulatory cytokine and secreted by regulatory T cells (Treg) in response to glucocorticoids. In reduced glucocorticoid response there is a failure of T-helper cells to secrete IL-10 [16].

Also, the macrophage migration inhibitory factor is a proinflammatory cytokine that has potent anti-glucocorticoid effects and has been correlated with many inflammatory diseases. MIF has also been involved in the glucocorticoid resistance in pulmonary diseases [16].

Therapeutic implications of glucocorticoid resistance by either selective glucocorticoid receptor agonists (SEGRAs or dissociated steroids) are more effective in trans-repression than trans-activation so have fewer adverse event. There are numerous therapeutic strategies to manage glucocorticoid-resistant diseases, but the most significant general approaches are to use another anti-inflammatory ("steroid-sparing") treatments or to reverse the molecular mechanisms of glucocorticoid resistance [16].

There are a number of alternative anti-inflammatory drugs now available to treat some glucocorticoid resistant. Several p38 MAPK inhibitors have been in clinical development and theoretically could be mainly effective in pulmonary disease with glucocorticoid resistance due to IL-2 and IL-4, as this is reversed in vitro by selective p38 MAPK inhibitors. Also, a further option for treating glucocorticoid resistance is a reversing glucocorticoid resistance. The oxidative stress has a significant role in reducing HDAC2 and leads to glucocorticoid resistance, antioxidants should also be effective [16].

2.6.3 Pulmonary fibrosis induced by bleomycin resistance to corticosteroid

Nettelbladt and Langenbach found that there was no impact of methylprednisolone treatment on bleomycin induced lung fibrosis in animal model. Also, prednisolone treatment had a limited effects on bleomycin- induced lung fibrosis in rats [17-18]. The TGF-B is important to the pulmonary inflammatory and fibrotic responses, then corticosteroid therapy administered in the advanced stages of the disease would likely not inhibit the TGF-B production by alveolar macrophages [19].

The relative resistance to corticosteroid therapy in pulmonary inflammatory and fibrotic responses seen in many human lung diseases may be caused by the corticosteroid insensitivity of TGF-B production by alveolar macrophages. This recommends that only at the early inflammatory stages, when infiltration of macrophages was significant, that corticosteroid therapy is of benefit [60-72]. However, at a later stage when alveolar macrophages are activated to secrete TGF-B, corticosteroids are ineffective. Activated alveolar macrophages obtained after bleomycin-induced pulmonary injury secreted increased quantities of TGF-B. Furthermore, the alveolar macrophage secretion of TGF-B is not inhibited by the existence of high concentrations of corticosteroids [19].

Hosoya T. and colleague found that no impact of corticosteroid in pulmonary fibrosis induced by bleomycin due to of interleukin-4 was not inhibited by nonselective glucocorticoid after glucocorticoid administration (1mg/kg/day) in mice model [20] Also, the IL-13 mediated myofibroblast differentiation was resistance to corticosteroid [4].

2.6.4 Anticoagulation (warfarin)

Stimulation of thrombin is early events after tissue damage. Thrombin encourages the differentiation of fibroblasts to a myofibroblast phenotype, rises proliferation of fibroblast, and improves the proliferative effect of fibrinogen on fibroblasts [73-89]. Thrombin is also a strong inducer of cytokines in fibrosis, including (transforming growth factor-β, connective tissue growth factor, platelet-derived growth factor (PDGF)), with encourages numerous of chemokines and proteins of extracellular matrix such as collagen, fibronectin, and tenascin. Treatment with warfarin leads to a decrease in the secondary outcome of IPF acute exacerbation-associated mortality. The anticoagulants are targeting specific coagulation factors on fibrosis signaling receptors may exert antifibrotic effect [21].

Limitations: The anticoagulants lack the benefit effect in fibrosis and increase the cause of death

with warfarin at interim analysis [22]. Previous study found that the use of anticoagulants in patients with fibrotic ILD is linked with increased rate of death. Another possibility is that warfarin may have deleterious effects that drive worse outcomes. The warfarin might have adverse effects that speed up progression of disease in fibrotic lung disease. Recommended potential mechanisms for increased harm with warfarin include alveolar hemorrhage, detrimental effects of inhibition of vitamin K-dependent clotting factors, or loss of beneficial effects of protein C on inflammation and remodeling [23].

2.6.5 Selective endothelin receptor antagonist (ambrisentan)

The endothelin receptors classified into two types; endothelin type A(ETA) receptors, which induce contraction of vessels (vasoconstriction) and are usually found on vascular smooth muscle cells, and the endothelin type B1 (ET-B1) receptors, located in the endothelial cells, which are known to promote the release of nitric oxide (NO)and prostacyclin to produce a vasodilating effect. ET-A receptors have also been shown to propagate epithelial-to-mesenchymal transition through intermediary cytokines, leading to a profibrotic state [24].

ET-B2 receptors antagonize ET-B1 receptors and vasoconstrict through an unknown mechanism. Clinically available endothelin receptor antagonists (ERAs) include selective ET-A antagonists (e.g., ambrisentan) and dual antagonists that affect both ET-A and ET-B receptors (e.g., bosentan and macitentan). Increased ET-A and ET-B receptor levels have been found in pulmonary fibrosis-affected fibrotic lung, and as such, both selective and dual antagonists have been investigated for potential benefit in treating patients with pulmonary fibrosis [24].

Limitations: Ambrisentan increased the progression of disease, evaluated as worsening respiratory function test such as DLCO or FVC, regardless of the presence or absence of pulmonary hypertension [24]. The observations in previous study reported that the evidence for ambrisentan as an ineffective treatment for patients with IPF The association of ambrisentan therapy with an increased risk for disease progression and respiratory hospitalization [24].

2.6.6 Pirfenidone

It is an oral antifibrotic drug. It has a role in regulation of profibrotic and proinflammatory cytokine cascades in vitro while decreasing proliferation of fibroblast and production of collagen in lung fibrosis in animal models. It also demonstrated a benefit to pirfenidone treatment in terms of a reduction in the rate of decline in VC and improved progression-free survival. In study, pirfenidone showed a reduction in decline of FVC during the 72-week treatment period. In other study did not show a benefit in the same outcome during the same period. Trails suggested improved mortality with pirfenidone. Pirfenidone decreased the rate of FVC decline [24].

Limitations: It has some adverse effect such as; photosensitivity, fatigue, stomach discomfort, and anorexia and some patients may not be willing to tolerate certain adverse effects even in the setting of treatment benefit [24]. In previous clinical trial, they failed to find a significant beneficial effect of pirfenidone over placebo in improving/stabilizing FVC, exercise capacity, symptoms, or skin disease [25].

2.6.7 Antacid

Above of 90% of patients of pulmonary fibrosis have gastroesophageal reflux disease (GERD). The GERD is the one of common risk factor of PF because it is leading to aspiration and micro-aspiration, which leads to pneumonitis, a mechanism that will caused worsen pulmonary fibrosis [24].

Antacid treatments such as proton pump inhibitors (PPIs) or histamine2 blocker receptor antagonists (H2RAs), can reduce the risk for micro-aspiration-associated lung injury or damage. Places a higher value on possible improved lung function and survival and the low cost of therapy and a lower value on the potential increased risk for pneumonia with antacid therapy. It is important to note that this recommendation applies to all patients with pulmonary fibrosis, as it is based on pulmonary fibrosis being the treatment indication, rather than abnormal GER [24].

limitations: It is not recommended used as monotherapy because it is just decreasing risks for GER. Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease as same mentioned in previous studies, there is no beneficial effect of antacid therapy in patients with IPF. Although clinicians might reasonably

offer antacid therapy to patients with IPF who have symptomatic gastro-esophageal reflux or off er fundoplication to those with uncontrolled reflux symptoms [26].

2.6.8 Selective tyrosine kinase inhibitor "Imatinib"

It is a selective tyrosine kinase inhibitor against platelet derived growth factor (PDGF) receptors. It is a strong suppressor of lung fibroblast into myofibroblast differentiation and proliferation, also, a suppressor of production of extracellular matrix via suppression of PDGF and TGF-b signaling [24].

limitations: There is increased the risk of adverse events in the imatinib. It is an expensive drug without beneficial effect in patients with pulmonary fibrosis to decrease progression of disease or decrease the cause the death [24].

Pervious study found that there was no benefit in DLCO, absolute change in FVC, and the distance walked using a 6-minute walk test. Although this study demonstrates imatinib was not an effective therapy for IPF [27].

2.6.9 Multiple tyrosine kinase inhibitors "Nintedanib"

The U.S. Food and Drug Administration approved nintedanib oral capsules to treat patients with chronic fibrosing (scarring) interstitial lung diseases (ILD) with a progressive phenotype (trait). It is the first FDA-approved treatment for pulmonary fibrosis that worsen over time.

It is a strong, orally available small-molecule intracellular inhibitor and indolinone-derived inhibitor of multiple receptor tyrosine kinases (RTKs)tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF) receptors and colony stimulating factor 1 receptor (CSF1R) tyrosine kinases, which may result in the induction of endothelial cell apoptosis, the reduction in tumor vasculature, the inhibition of tumor cell proliferation and migration, and antifibrotic activity in pulmonary fibrosis [24].

In addition, nintedanib also binds to and inhibits members of the Src family of tyrosine kinases, including Src, Lck and Lyn, and fms-like tyrosine kinase 3 (FLT-3). VEGFR, FGFR, PDGFR and CSF1R RTKs play significant roles in tumor angiogenesis, tumor cell proliferation and metastasis, as well as pulmonary fibrosis [28].

3. CONCLUSION

Corticosteroids are gold standard medication for inflammatory and immune diseases but there are many of diseases resistance to corticosteroid such as pulmonary fibrosis and to reverse this resistant used another alternative anti-inflammatory.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It’s not applicable.

ETHICAL APPROVAL

It’s not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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