Chapter 10
Pharmacotherapy of IPF (Corticosteroids, Immunosuppressants, Etc.)

Are These Actually Effective? Ineffective? Harmful?

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Abstract There was no evidence showing the usefulness of corticosteroid and immunosuppressant with anti-inflammatory effects for the treatment of idiopathic pulmonary fibrosis (IPF). This therapy may induce acute exacerbation associated with dose reduction and side effects such as a complicated infection. Therefore, the treatment with corticosteroid and immunosuppressant is not recommended in definite IPF patients in an official ATS/ERS/JRS/ALAT statement (evidence-based guidelines for diagnosis and management of IPF).

However, the usefulness of the combination therapy with a small amount of corticosteroid and immunosuppressant or antifibrotic agents is still unknown. It cannot be completely denied that this combination therapy becomes one of the therapies as conditional recommendation for the moment.

Keywords Idiopathic pulmonary fibrosis • Corticosteroid • Immunosuppressant

10.1 Introduction

Because it is thought to be important to control "lung injury caused by chronic inflammation of alveolar septa and the process of becoming fibrotic," historically, a corticosteroid and immunosuppressant with anti-inflammatory effects have been administered as the treatment strategy for idiopathic pulmonary fibrosis (IPF) [1–3].

However, in low-evidence studies performed before 2000 [4, 5], not all IPF patients were given combination treatment of a corticosteroid and immunosuppressant. In addition, patients with nonspecific interstitial pneumonia (NSIP) or secondary interstitial pneumonia might have been included in the studies showing that corticosteroid therapy was effective. In the ATS/ERS international consensus statement in 2000 [6], the combination of a relatively small amount of

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corticosteroid and immunosuppressant has been proposed as a therapy for IPF. Additionally, because combination therapy with immunosuppressant was effective compared with corticosteroid monotherapy which was shown to be less effective [7, 8], the combination of a corticosteroid and immunosuppressant is designated as a proposed therapy in guidelines on the diagnosis and therapy of idiopathic interstitial pneumonias (IIPs) published in Japan in 2004. The combination of an immunosuppressant with corticosteroid tapering or corticosteroid alternate-day therapy has been provided as a specific treatment for IPF until the revised second edition published in 2008 [9].

Moreover, in recent years, a major pathological condition of IPF that produces resistance to corticosteroid therapy is believed to be "repetitive alveolar epithelial cell injury and subsequent abnormal lesion repair, which induce proliferation of fibroblasts and deposition of extracellular matrix," by the development of molecular techniques used in studies of pathophysiological conditions, resulting that an antifibrotic therapy is playing a central role [10–12].

This chapter describes functions of treatment with a corticosteroid and immunosuppressant in the medical care of IPF patients in the stable phase based on the latest evidences.

10.2 Corticosteroid and Immunosuppressant for the Treatment of IPF from the Perspective of the Latest Guidelines

In the evidence-based guidelines for diagnosis and management of IPF [13] prepared by the ATS/ERS/JRS (the Japanese Respiratory Society)/ALAT (the Latin American Thoracic Association) in 2011, the treatment recommendations were determined based on the previous evidence-based studies. These guidelines recommended that patients with IPF should not be treated with corticosteroid monotherapy, cyclosporine A therapy, and the combination of corticosteroid with immunosuppressant (azathioprine or cyclophosphamide) (strong recommendation, very low-quality evidence). A three-drug combination therapy of corticosteroid, azathioprine, and oral N-acetylcysteine (NAC) was not recommended in the majority of IPF patients, but this therapy may be a reasonable choice in a minority (weak recommendation, low-quality evidence) (Table 10.1). However, according to an interim report of the clinical trial with three arms of steroid/azathioprine/oral NAC, NAC monotherapy, and placebo (PANTHER-IPF) [14], because elevations in the mortality rate, and hospitalization, and acute exacerbation had been reported, the previous recommendation was revised, and the recommendation against the use of the three-drug combination therapy with corticosteroid, azathioprine, and oral NAC for the treatment of IPF is strong in 2015 guidelines [15].

Taken together, there was no evidence showing the usefulness of the combination of corticosteroid and immunosuppressant for the treatment of IPF. Considering

Table 10.1 Evidence-based treatment

Treatment	Recommended	Strength of recommendation	Quality of evidence
Pharmacologic therapies			
Corticosteroid monotherapy	No	Strong	⨁◯◯◯
Colchicine	No	Strong	⨁◯◯◯
Cyclosporine A	No	Strong	⨁◯◯◯
Corticosteroid + immunomodulatory	No	Strong	⨁◯◯◯
Corticosteroid + azathioprine + acetylcysteine	Majority – no	Weak	⨁⨁◯◯
	Minority – may be a reasonable choice		
2015 Guidelines	No	Strong	

2011 Guidelines for the diagnosis and management of IPF. An ATS Pocket Publication (modified)

the possibility that this therapy may induce acute exacerbation associated with dose reduction and side effects such as a complicated infection which occurs with long-term usage, the treatment with corticosteroid and immunosuppressant is not recommended in definite IPF patients.

10.3 Therapy for IPF in Our Clinical Practice

A study that aimed at elucidating the actual medical practice concerning IPF in Japan entitled "A prospective investigation research for diffuse pulmonary disease, Project on Measures for Intractable Diseases, Health and Labour Science Research Grant" was registered on the Internet, and a prospective epidemiological study was conducted [12]. Information obtained from a multicenter study including the therapeutic regimen, clinical findings, and the clinical course of patients with IIPs including IPF was actively entered in a database on the Internet. As a result, 321 IPF patients from 19 medical facilities were registered. Regarding the therapeutic regimen for IPF patients and a change in the regimen (see Fig. 10.1), the majority of IPF patients were untreated (78.7 %) by the end of fiscal year 2008 when pirfenidone was approved, but the untreated rate among IPF patients decreased by 44.6 % between 2009 and the end of fiscal year 2013. Pirfenidone has been used as a therapy for IPF patients (32.9 % between 2009 and the end of fiscal year 2013) including pirfenidone monotherapy (17.4 %), and therefore this medication plays a key role in the treatment of IPF in Japan. On the other hand, the use of corticosteroid monotherapy for IPF patients showed a slight increase from 6.2 to 7.5 %; likewise, the use of the combination of corticosteroid and immunosuppressant slightly increased from 11.2 to 13.1 %. These results show that the combination of a corticosteroid and immunosuppressant is used conditionally as symptomatic therapy for IPF in our medical practice with awareness of the side effects of each medication.

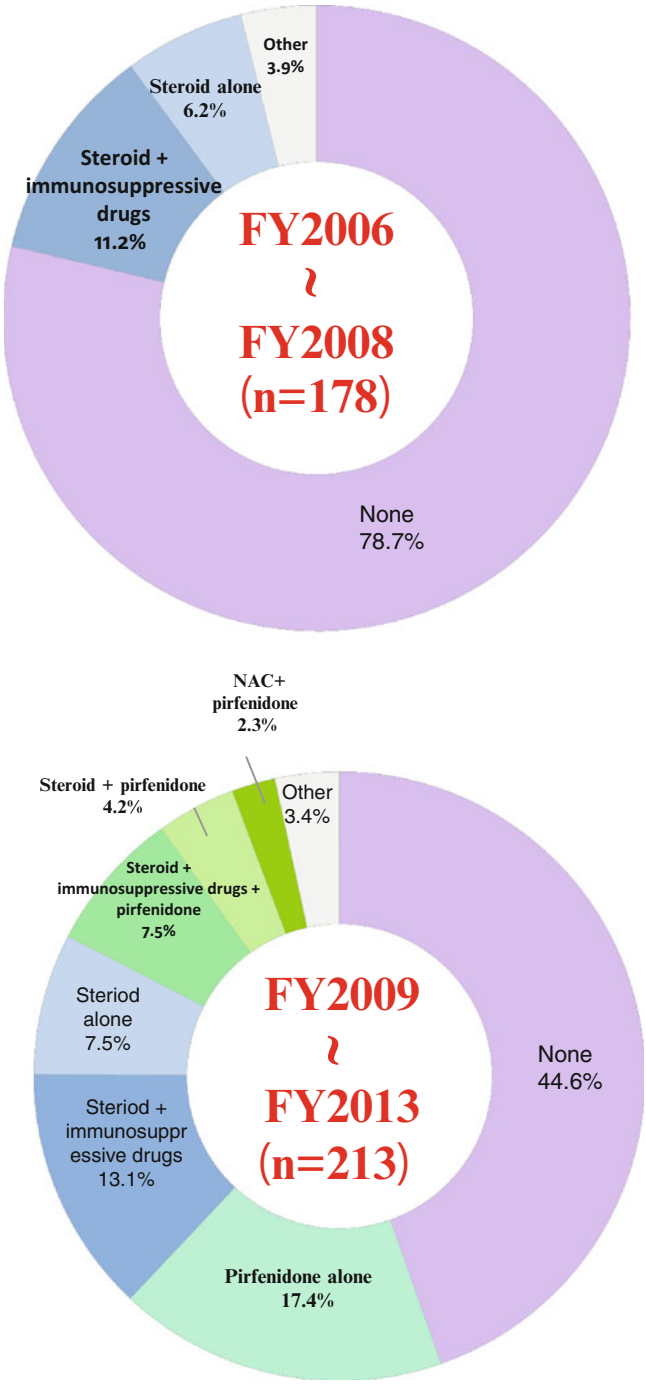

Fig. 10.1 The treatments and their changes in IPF

10.4 Pharmacological Effects and Side Effects from the Use of Corticosteroid and Immunosuppressant

10.4.1 Corticosteroids

The anti-inflammatory effects of corticosteroids are well known for their genomic mechanism producing biological actions. After the corticosteroids form complexes with glucocorticoid receptors (GCRs) inside the cytoplasm, the complexes translocate to the nucleus and bind to glucocorticoid-response elements on DNA. Once GCRs that had translocated into the nucleus bind to negative glucocorticoid-response element, the mRNA transcription of various cytokines involved in inflammation is inhibited. On the other hand, when GCRs translocate into the nucleus and bind to positive glucocorticoid-response element on DNA, the mRNA transcription of anti-inflammatory proteins is upregulated. The binding of transcription factors including nuclear factor-κB and AP-1 to DNA is inhibited, resulting in interference of cytokine production [16]. The amount of corticosteroid that would saturate corticosteroid receptors in an adult human is approximately 60 mg of prednisolone, although there are individual differences. In contrast, high-dose corticosteroid therapy is thought to act through a non-corticosteroid receptor-mediated mechanism, so-called non-genomic mechanism [17], which is entirely different from the genomic mechanism and has an onset of effect between a few seconds and a few minutes. Although the details are unknown at this time, there are two kinds of non-genomic mechanisms: nonspecific effects that directly act on cell membrane fluidity and specific effects that act on a specific receptor. Corticosteroid pulse therapy can be expected to have stronger genomic and non-genomic effects and have an impact on inflammatory cells, alveolar epithelial cells, T lymphocytes, vascular endothelial cells, etc. [18, 19]. Meanwhile, because corticosteroids do not inhibit the production of basic fibroblast growth factor and transforming growth factor-β (TGF-β) in bleomycin-induced murine pulmonary fibrosis [20], they have no antifibrotic actions. The following side effects of corticosteroids are important: diseases induced by infectious diseases (particularly tuberculosis, fungus, cytomegalovirus, Pneumocystis pneumonia, etc.), peptic ulcer, diabetes, mental deterioration, hypertension, secondary adrenocortical insufficiency, osteoporosis, aseptic necrosis of the femur and others, myopathy, glaucoma, cataract, thrombosis, endocrine abnormality, and so on. Because the above major side effects influence disease prognosis, whether the therapeutic effect is beneficial to the patient or not needs to be carefully pondered when such a side effect occurs. In addition, a decision must be made as to whether patients will continue the therapy with corticosteroid, reduce the dose, or discontinue this therapy. When a corticosteroid is administered for a long period of time, the combined treatment of sulfamethoxazole and trimethoprim is necessary to prevent Pneumocystis pneumonia. Because postmenopausal women and elderly people are vulnerable to the development of osteoporosis and compressed fracture, a medication such as bisphosphonate is also required. In contrast, minor side effects of corticosteroid administration include

hirsutism, acne, moon-shaped face, extravasation of blood into the skin, purpura, and so on, but these side effects are sometimes not severe, and the physician may not recommend reducing the dose or discontinuing the drug.

10.4.2 Immunosuppressants

Generally, an immunosuppressant is used for the treatment of various interstitial pneumonias other than IPF in the following cases: patients who have no response to corticosteroids, those who experienced severe side effects of corticosteroid, and those who are at high risk of developing side effects with corticosteroid. In the United States and Europe, cyclophosphamide and azathioprine are often used for treatment, but cyclosporine A is also used in Japan.

10.4.2.1 Cyclophosphamide

Cyclophosphamide is classified as an alkylating compound that is activated by hepatic microsomal enzymes and exhibits pharmacological action. The inhibitory effects of cyclophosphamide on DNA synthesis act on the cell cycle in a nonspecific manner. Cyclophosphamide shows a stronger inhibitory action against B lymphocytes than T lymphocytes. The general dosage required for cyclophosphamide is 1.0–2.0 mg/kg/day (ideal body weight, highest dose: 150 mg/day). The medication is initiated at 50 mg/day and increased by 25 mg every 7–14 days as needed. Because the onset of the therapeutic effect is usually more than 3 months after starting this medication, the medication needs to be continued for at least 6 months or longer as long as there are no severe side effects. Some side effects of cyclophosphamide are bone marrow suppression, hemorrhagic cystitis, second primary cancer, hair loss, a feeling of sickness, stomatitis, diarrhea, and hepatic impairment associated with cholestasis. Pulmonary fibrosis has also been reported although it is rare. The medication is suspended or the dose is reduced by half when the white blood cell count falls below 4,000/mm^3 or platelet count falls below 100,000/mm^3. Patients drink adequate fluids to prevent hemorrhagic cystitis, establish urine flow, and take a urine test monthly. When hemorrhagic cystitis occurs, the medication is discontinued.

10.4.2.2 Azathioprine

Azathioprine, which is classified as an antimetabolic drug, is transformed into 6-mercaptopurine in the liver and is later physiologically activated. Azathioprine is a medication that acts specifically on the cell cycle and inhibits purine synthesis by acting on the DNA synthetic phase. Its immunosuppressive effect is mainly caused by suppression of the proliferation of T lymphocytes. The general dosage

required for azathioprine is 2.0–3.0 mg/kg/day (ideal body weight, highest dose: 150 mg/day). The medication is initiated at 50 mg/day and the dose is increased by 25 mg every 7–14 days as needed. Side effects are bone marrow suppression, a feeling of sickness, vomiting, gastrointestinal symptoms such as diarrhea, and hepatic impairment. The medication is suspended or its dose is reduced by half when the white blood cell count falls below 4,000/mm^3 and the platelet count falls below 100,000/mm^3. Patients undergo a hepatic function test monthly, and the medication is later suspended, or its dose is reduced when the measured value of AST and ALT reaches more than three times the upper limit of a normal hepatic function.

10.4.2.3 Cyclosporine A

Cyclosporine A binds with cyclophilin in the cytoplasm and exerts an effect by suppressing the proliferation and activation of T lymphocytes [21, 22]. Additionally, cyclosporine A improves corticosteroid resistance through inhibition of p-glycoprotein involved in drug resistance. There is a report that cyclosporine inhibits late-onset hypersensitive reaction, transplant rejection, and T-lymphocyte-dependent antigen-antibody reaction. On the other hand, another study reported that cyclosporine induces TGF-β [23]. However, further analysis is needed because there is a new study indicating that cyclosporine inhibits TGF-β secretion and has antifibrotic actions against muscle fibroblasts [24, 25]. Because the difference between the critical region and blood level that can exert an immunosuppressive effect is small in cyclosporine, the dose is determined by monitoring its blood level in whole blood. The medication is initiated at 3.0 mg/kg/day twice daily, and the level 12 h after administration is approximately 100–150 ng/mL. There are two issues that should receive special attention: one is that oral absorption varies considerably among individuals, and the other is that it interacts with many drugs (calcium antagonist, macrolide antimicrobial drug, and antifungal drug increase blood levels). Side effects are kidney failure (dosage dependent), hypertension, gingival hypertrophy, neurological symptoms (headache, tremulousness, and dysesthesia), hirsutism, and so on. Periodic observation of renal function is needed during treatment with cyclosporine. In addition, although the onset is relatively less frequent, special attention needs to be paid to infection by viruses (cytomegalovirus, herpes simplex virus, chicken pox, herpes zoster virus, and Epstein-Barr virus), protozoa, fungus, and so on.

10.5 The Remaining Challenges

As described earlier, there is no evidence that shows the usefulness of corticosteroid or immunosuppressant as a therapy for definite IPF [13, 26, 27]. However, it's sometimes difficult to make the diagnosis of IPF among many differential

diagnoses including chronic hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and so on in medical practice. Concretely speaking, therapy with a corticosteroid and immunosuppressant can be considered in the following cases (Table 10.2) [9]: a case in which image findings and subjective symptoms worsen compared with a few months prior, a case in which a honeycomb lung is not visibly found by high-resolution computed tomography, a case in which the number of lymphocytes in bronchoalveolar lavage fluid is increasing, and a case in which a diagnosis on the basis of pathological findings in other IIPs such as NSIP and cryptogenic organizing pneumonia is confusable. There are also many unsolved issues in the usage and rate of reduction of the dose of corticosteroid and immunosuppressant.

Because the dosage regimen for corticosteroid therapy conducted in the PANTHER trial [14], which differs from what we have experientially determined in Japan, is a regimen that reduces the dosage rapidly, it is too soon to decide a total ban on medication based on only the result from this clinical trial. In Japan, as a prospective multicenter therapeutic study of a clinical trial of revolutionary therapy, a comparative trial between the groups of combination therapy with cyclosporine and corticosteroid (10–20 mg) and that with cyclophosphamide and corticosteroid (10–20 mg) for IPF has been conducted since 2005 [28]. According to this study, the amount of decrease in forced vital capacity for 48 weeks was 78 mL (cyclosporine and corticosteroid) and 87 mL (cyclophosphamide and corticosteroid) in each of the combination therapy groups, which showed no significant difference; therefore, the combination therapy with cyclosporine is non-inferior. In addition, in the recent clinical trial for a new inhibitor of fibrosis, nintedanib [29], a small amount of corticosteroid is concurrently administered to approximately 20 % of patients in each group.

In conclusion, at present, the usefulness of the combination therapy with a small amount of corticosteroid and immunosuppressant or antifibrotic drugs is still unknown. Therefore, it cannot be completely denied that this combination therapy becomes one of the options as conditional recommendation.

Table 10.2 Cases of IPF in which the use of corticosteroid and immunosuppressant can be considered

1.	Image findings and subjective symptoms worsen compared with a few months ago
2.	Honeycomb lung is not visibly found by high-resolution computed tomography
3.	The number of lymphocytes in bronchoalveolar lavage fluid is increasing
4.	A diagnosis on the basis of pathological findings in other IIPs such as NSIP and cryptogenic organizing pneumonia is confusable

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