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Efficacy and safety of dual filtration plasmapheresis combined with biological agents in active refractory rheumatod arthritis

A retrospective cohort study

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Abstract

To investigate the effectiveness of dual filtration plasmapheresis (DFPP), a novel blood purification treatment, as a rapid and sustained disease-modifying therapy for active refractory rheumatoid arthritis (RA).

A retrospective cohort study had been conducted. One hundred fifty three patients aged 18 years or older with active refractory RA were treated with DFPP combined with infliximab (IFX), IFX, or glucocorticoid (GC), all the above treatments were combined with methotrexate (MTX).

Baseline characteristic of the 153 patients (DFPP: n = 53; IFX: n = 51; GC: n = 49) were similar across groups. The remission rate of CDAI (SDAI) in the DFPP treatment group was significantly higher than that of the IFX and GC group after 3 months of treatment. The remission rate of DFPP treatment group was above 50%, while in IFX and GC group, the rate of CDAI (SDAI) remission was 41.2% (37.3%) and 22.4% (14.2%) after 3 months of treatment.

A combination of DFPP and biological agents can quickly induce remission or low disease activity of active refractory RA.

Abbreviations: ACR = American Rheumatism Association, CDAI = clinical disease activity indices, CRP = C reactive protein, DAS28 = Disease Activity Score using 28-joint counts, DFPP= dual filtration plasmapheresis, DMARDs = disease-modifying antirheumatic drugs, EGA = global evaluator assessment of disease activity, ESR = erythrocyte sedimentation rate, GC = glucocorticoid, HAQ = physical function by Health Assessment Questionnaire, HCQ = hydroxychloroquine, IFX = infliximab, IL = interleukin, LDA = low disease activity, MTX = methotrexate, PGA = global patient assessment of disease activity, RA = rheumatoid arthritis, REM = remission, SASP = sulfasalazine, SDAI = simplified disease activity indices, SJC28 = numbers of swollen tender joints by using a 28-joint count, T2T = treat-to-target, TJC28 = numbers of tender joints by using a 28-joint count, TNF = tumor necrosis factor, VAS = visual analogue score.

Keywords: biological agents, dual filtration plasmapheresis, immunoadsorption, rheumatoid arthritis

1. Introduction

RA is a systemic inflammatory autoimmune disease affecting joints and internal organs. Patients with RA have a notable increased risk of experiencing functional disability with the prolongation of the course of the disease.[1] The continued non-remission of RA will lead to further destruction of cartilage and bone in joints which results in joint deformities and loss of function, decreased quality of life, and ultimately the loss of labor.[2] It is revealed that there was a higher prevalence of functional disability in joints disease compared with other diseases or traffic accidents in China.[3] Current treat-to-target (T2T) recommendations suggest that RA

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patients should strive for clinical remission as a goal. The patients can benefit the most from the clinical remission (REM) as soon as possible. But for patients with longstanding disease and inadequate response to conventional therapy, low disease activity (LDA) is also considered as an acceptable alternative.[4]

Due to the use of conventional synthetic disease-modifying antirheumatic drugs (DMARDs), manufactured and biological DMARDs, the prognosis and clinical outcome in RA has improved significantly over the last 10 to 20 years. But even in the case of many targeted biological agents and analogue natural therapies, studies showed that the clinical remission rate of RA is still 50% or so.[5] The figure is even lower in China. It is estimated that in the 10 years of RA definitive diagnosis and treatment, 30% of the patients are disabled.[6] Therefore, there is an urgent need to seek more effective remedies for RA to improve the clinical remission rate and prevent the loss of the labor force.

DFPP is a blood purification technique developed in recent years. It is a method of selective plasmapheresis, pioneered by Agishi et al in Japan (in the 1980s). DFPP is also an immune adsorption technology. And it was first used to treat with RA in 1994.[7] The effect of this therapy is to remove high molecular weight substances, mainly immunoglobulins, and lipids, from plasma by using molecular sieve effect of hollow fiber membranes with 2 different pore sizes. Recent studies show that DFPP has an excellent therapeutic effect on RA, especially in patients with severe RA.[8,9] It is also mentioned in the latest guidelines as an alternative treatment for RA.[10]

Infliximab (IFX) has been widely used in the clinic. It has an excellent therapeutic effect on RA for a long time and has abundant clinical data. However, there are few reports on the efficacy of combined immunoadsorption with IFX in patients with active refractory RA. Therefore, this study will verify whether the combination of immunosorbent therapy and IFX therapy can rapidly alleviate active refractory RA or achieve low disease activity.

2. Materials and methods

2.1. Patients

A retrospective cohort study of 153 patients with active refractory rheumatic diseases was conducted. All of the patients were inpatients at the Department of Rheumatology in the Second Affiliated Hospital of Dalian Medical University from August 2016 to September 2018. Patients included 115 women and 38 men, between the ages of 20 and 71 years. Disease duration was from 12 months to 11 years. All patients met the 1987 American Rheumatism Association (ACR) classification criteria for RA. Active means: 3 or more swollen joints; 8 or more tender joints; the time of morning stiffness≥ 60 minutes; erythrocyte sedimentation rate (ESR)≥ 28 mm/hour or C reactive protein (CRP) more than 1.5 times the upper limit of normal; HAQ ≥1.0. Refractory means: All of the patients were still active after a standard dose of methotrexate (MTX) plus sulfasalazine (SASP) plus hydroxychloroquine (HCQ) for more than 6 months. All patients underwent a PPD test, chest X-ray, and t-spot to exclude latent tuberculosis infection. This study also excluded acute or chronic infection, liver and kidney damage, cardiovascular and lung disorders, pregnancy, breastfeeding women, exclude other connective tissue diseases.

This study was approved by the ethics committee of the Second Affiliated Hospital of Dalian Medical University (2017100).

2.2. Treatment

Patients were evaluated at baseline and 1, 3, 6 months after treatment. One hundred 4 patients received IFX (intravenous injections of 3 mg/kg IFX at weeks 0, 2, and 6, and after that, the treatment is administered by infusion at every 8 weeks) plus MTX (10 mg once a week PO). Fifty three of the 104 patients were treated with DFPP twice, the next day after the second DFPP they were treated with IFX and MTX (DFPP group). Fifty one of the 104 patients received IFX plus MTX treatment (IFX group). Forty nine patients received step-down prednisolone plus MTX (10 mg once a week PO) (GC group). All patients were taking 1 to 2 nonsteroidal anti-inflammatory drugs.

DFPP treatment: Deep venous catheterization was established before DFPP. After anticoagulation, the OP-08W Membrane Plasma Separator Manufactured (Asahi Kasei Corporation, Japan) and the EC-30W Plasma Separator (Asahi Kasei Co, Tokyo, Japan) were used for double plasma exchange. The OP-08W Immunosorbent Column (Asahi Kasei Co, Tokyo, Japan) was used to adsorb the immunoglobulin. The DFPP treatments were conducted twice a week. Each DFPP treatment lasted 2 to 2.5 hours. The total amount of filtered plasma is about 2000 ml, with the blood flow rate as 80 to 100 ml/minute.

2.3. Disease activity assessment

Clinical data of the patients were collected, including age, sex, and course of the disease. Variables regularly documented include CRP, ESR, numbers of swollen, and tender joints by using a 28-joint count (SJC28, TJC28); global patient assessment of disease activity (PGA), comprehensive evaluator assessment of disease activity (EGA), and physical function by Health Assessment Questionnaire (HAQ). Composite indices, such as the clinical and simplified disease activity indices (CDAI, SDAI) and the Disease Activity Score using 28-joint counts (DAS28-ESR) were calculated based on these variables. The CDAI (SDAI) is the arithmetic sum of SJC+TJC+PGA+EGA (SJC+TJC+PGA +EGA+CRP), whereby the 28 joint counts are used for joint assessment, the global evaluations are employed in cm rather than mm, and CRP as mg/dl.[11] DAS28-ESR is according to formulae reported before.[12]

Cut-points for the CDAI (SDAI) were applied as follows: LDA >2.8 and ≤ 10 (>3.3 and ≤ 11), REM ≤ 2.8 (≤ 3.3).

2.4. Safety evaluation

Any discomfort symptoms and abnormal laboratory findings during the treatment of the patient were recorded. The items included a routine blood test, liver function, and renal function.

2.5. Statistical analysis

SPSS Statistics v.20 (SPSS, Inc, Chicago, IL, USA) was used for statistical analyses. Data are expressed as means ± SD. Comparisons between groups were evaluated by using the independent *t* test or analysis of variance (ANOVA). The conditions of values <0.05 were considered as statistically significant.

3. Result

3.1. Patient characteristics

Baseline characteristics were similar across the 3 treatment groups, including age, the proportion of females, and symptom

Table 1

Baseline patient characteristics.

Characteristic	DFPP Group n = 53	IFX Group n = 51	GC Group n = 49
Age, year, mean ± SD	54.75 ± 13.09	55.69 ± 13.34	58.96 ± 10.66
Women, n (%)	41 (77.4)	39 (76.4)	38 (77.6)
SJC28, mean ± SD	8.95 ± 3.99	8.00 ± 4.40	7.45 ± 4.82
TJC28, mean ± SD	14.22 ± 5.51	12.02 ± 4.54	12.45 ± 5.40
VAS, cm, mean ± SD	7.03 ± 1.12	7.10 ± 143	7.01 ± 1.21
PGA, cm, mean ± SD	7.13 ± 1.45	7.04 ± 1.26	7.17 ± 1.31
EGA, cm, mean ± SD	5.75 ± 1.44	5.74 ± 1.62	5.86 ± 1.41
HAQ, mean ± SD	1.39 ± 0.71	1.00 ± 0.68	1.03 ± 0.76
DAS28, mean ± SD	6.10 ± 0.51	6.12 ± 0.88	6.21 ± 0.80
ESR, mm/h, mean ± SD	59.28 ± 28.95	52.64 ± 32.79	47.08 ± 28.20
RF, positive n (%)	46 (86.8)	45 (88.2)	40 (81.6)
CRP, mg/l, mean ± SD	36.32 ± 32.94	37.47 ± 41.38	31.17 ± 31.69

CRP = C reactive protein, DAS28 = Disease Activity Score using 28-joint counts, DFPP = dual filtration plasmapheresis, EGA = global evaluator assessment of disease activity, ESR = erythrocyte sedimentation rate, GC = glucocorticoid, HAQ = physical function by Health Assessment Questionnaire, IFX = infliximab, PGA = global patient assessment of disease activity, SJC28 = numbers of swollen tender joints by using a 28-joint count, TJC28 = numbers of tender joints by using a 28-joint count, VAS = visual analogue score.

duration (Table 1). The mean duration of treatment was identical for the 3 drugs.

3.2. Clinical efficacy

Significantly, more DFPP than IFX and GC group patients reached the primary endpoint. Three out of 53 patients of the DFPP group reached CDAI (SDAI) remission at M1 (Table 2), more than IFX and GC group. Further, until the M3, there were patients of the latter 2 groups reached CDAI (SDAI) remission. This ascendancy held on. At M6, more than half of the patients of the DFPP group reached CDAI (SDAI) remission. The remission rates of FX group and GC group were 41.2% (37.3%) and 22.4% (14.2%), respectively (Table 2). All these 3 treatments can improve the clinical indicators of refractory RA patients.

The clinical indicators of the 3 groups improved significantly after treatment. VAS score, ESR level, and CRP level decreased significantly compared with baseline (Table 3). In the improvement of joint symptoms, VAS score, HAQ score, the DFPP group was markedly better than IFX and GC group at M1, suggesting that the effect of DFPP treatment was faster than that of the 2 other groups. ESR CRP in the DFPP group was significantly lower than that in the other 2 groups at 6 months. The comparison of SJC28, TJC28, VAS score, PGA, and EGA score showed there was no significant difference in joint symptoms between the DFPP group and IFX group, but HAQ score, ESR and CRP were significantly lower than those of the other 2 groups at M6 (Table 3).

With the prolongation of treatment time, the remission rate of patients increased gradually. The effect of DFPP treatment was better than that of the other 2 groups at M1, M3, M6 (Fig. 1A). Patients were grouped according to age, sex, and course of the disease. The results showed that the younger the patients and the shorter the course of the disease, the better response to DFPP treatment. DFPP is the most effective treatment for patient over 30 years old and patients with a course of more than 10 years (Fig. 1B, C). Male patients responded better to the 3 treatments than female patients (Fig. 1D).

3.3. Adverse events

In the clinical observation, there were no significant adverse events in the 3 groups after treatment. In the GC treatment group, 14 cases of adverse events occurred after the treatment of 6 months, including 4 cases of oral ulcers and 10 cases of abnormal liver function. No oral ulcers but 4 transfusion reactions (slight rash and pruritus) occurred in the IFX group. There were 6 cases of adverse events in the DFPP group, 2 cases were transfusion reactions (mild rash) of IFX, and 4 cases of oral ulcers. No serious adverse events occurred in the DFPP treatment. From the frequency of adverse events, the difference between the 3 groups in the incidence of adverse events was not statistically significant ($P > .05$).

4. Discussion

The T2T concept has become increasingly adopted in RA. Remission is recommended as the primary therapeutic aim. LDA is an acceptable alternative, particularly in patients with longstanding disease, for whom remission may not be realistic.[10] Refractory RA patients usually have the longstanding disease and rapid progress in condition. The treatment of refractory rheumatoid arthritis has been a problem for rheumatoid arthritis for decades.

The use of biological agents has led to faster remission in patients with RA, which significantly improved the prognosis of patients with RA.[13] There are many kinds of biological agents for RA including tumor necrosis factor (TNF)-α inhibitors,[14,15] interleukin (IL)-1 inhibitors,[16,17] T cell activation, inhibition of small molecule like tofacitinib etc.[18] Contrast with the advent of RA biological drugs, the remission rate of RA treatment was improved, but not as ideal as imagined. A sizeable epidemiological survey led by Professor Li from Peking University People's Hospital showed that the clinical remission rate of Chinese RA patients was less than 10%, which was far lower than the clinical remission rate of 50% of patients with RA abroad. In this case of low disease remission rate, Chinas RA patients will have nearly 50% of the rate, due to the progress of RA disease, resulting in smaller labor force.[19,20]

Table 2

The REM and LDA rates (%) at different time points of the 3 groups.

	DFPP Group (n = 53)			IFX Group (n = 51)			GC group (n = 49)		
	CDAI	SDAI	DAS28-ERS	CDAI	SDAI	DAS28-ESR	CDAI	SDAI	DAS28-ESR
Month 1	5.6 (3)	1.8 (1)	13.2 (7)	0	0	9.8 (5)	0	0	0
Month 3	35.8 (19)	33.9 (18)	43.3 (23)	21.6 (11)	15.7 (8)	35.2 (18)	14.3 (7)	12.2 (6)	20.4 (10)
Month 6	60.4 (32)	56.6 (30)	69.8 (37)	41.2 (21)	37.3 (19)	50.9 (26)	22.4 (11)	14.2 (7)	40.8 (20)

Cut-points for the CDAI (SDAI) were applied as follows: REM ≤2.8 (≤3.3), LDA > 2.8 and ≤10 (>3.3 and ≤11). DAS28-ESR≤2.6 were considered to achieve REM and DAS28-ESR≤2.6 were considered to achieve LDA.

CDAI = Clinical Disease Activity Index, DAS28 = Disease Activity Score using 28-joint counts, LDA = low disease activity, REM = remission, SDAI = Simplified Disease Activity Index.

Table 3

Changes of observation indexes in 3 groups after treatment.

	DFPP Group (n=53)			IFX Group (n=51)			GC group (n=49)		
	Month 1	Month 3	Month 6	Month 1	Month 3	Month 6	Month 1	Month 3	Month 6
SJC28, mean±SD	0.68±1.07$^{\Delta\triangle\blacktriangle}$	0.24±0.66*	0.45±0.96*	2.21±3.14$^{\triangle}$	1.16±2.68	0.45±0.14	2.23±2.54*	1.92±3.56$^{\triangle\blacktriangle}$	1.38±2.28*
TJC28, mean±SD	2.8±2.95$^{\Delta\triangle\blacktriangle}$	2.74±4.02	2.48±2.64	4.91±4.49$^{\triangle}$	3.12±3.72*	2.70±4.12	4.81±5.26*	4.9±4.92*	3.6±3.16
VAS, cm, mean±SD	2.54±1.6$^{\Delta\triangle\blacktriangle}$	1.76±1.61$^{\triangle\blacktriangle}$	2.00±1.53$^{\triangle\blacktriangle}$	3.78±1.49$^{\triangle}$	2.65±1.62*	1.9±2.07*	4.12±2.41*	4.05±2.60$^{\triangle\blacktriangle*}$	3.77±3.05$^{\triangle\blacktriangle*}$
PGA, cm, mean±SD	2.52±1.35$^{\Delta\triangle\blacktriangle}$	2.44±1.54$^{\triangle\blacktriangle}$	1.92±1.78	3.82±1.52$^{\triangle}$	2.24±1.36*	3.03±1.58*	3.74±2.12*	3.58±1.99$^{\triangle\blacktriangle*}$	2.12±1.63*
EGA, cm, mean±SD	2.19±1.4$^{\Delta\triangle\blacktriangle}$	2.10±1.21$^{\triangle\blacktriangle}$	1.72±1.17$^{\triangle\blacktriangle}$	3.71±1.48$^{\triangle}$	2.33±1.14*	2.10±1.52*	3.96±1.98*	3.25±1.79$^{\triangle\blacktriangle*}$	2.8±1.57$^{\triangle\blacktriangle*}$
HAQ, mean±SD	0.51±0.56$^{\Delta\triangle\blacktriangle}$	0.11±0.34$^{\triangle\blacktriangle}$	0.45±0.72$^{\triangle\blacktriangle}$	0.76±0.67$^{\triangle}$	0.34±0.53*	0.23±0.46*	0.93±0.77*	0.94±0.86$^{\triangle\blacktriangle*}$	0.90±0.88$^{\triangle\blacktriangle*}$
ESR, mm/h, mean±SD	30.4±26.19	9.77±8.55$^{\triangle\blacktriangle}$	7.42±9.26$^{\triangle\blacktriangle}$	43.03±30.11	24.9±33.7	9.7±14.01*	34.35±43.16	47.8±78.9$^{\triangle\blacktriangle}$	41.02±29.67$^{\triangle\blacktriangle*}$
CRP, mg/l, mean±SD	18.13±42.89	27±21.17	23.30±16.28	30.28±37.43	35.94±29.68	29.88±20.75	36.17±60.41	27.68±23.78	27.35±13.85

CRP = C reactive protein, DFPP = dual filtration plasmapheresis, EGA = global evaluator assessment of disease activity, ESR = erythrocyte sedimentation rate, GC = glucocorticoid, HAQ = physical function by Health Assessment Questionnaire, IFX = infliximab, PGA = global patient assessment of disease activity, SJC28 = numbers of swollen tender joints by using a 28-joint count, TJC28 = numbers of tender joints by using a 28-joint count, VAS = visual analogue score.

In active refractory RA patients, the activated immune status is lasting. The pathogenic antibodies and inflammatory factors are being produced in large numbers. The traditional oral medicine mechanism mostly inhibits abnormal immunity, the action of steroids at requires a long time. In recent years, more and more studies show that the development of new immune adsorption technology can quickly remove the pathogenicity antibody and inflammatory factors to break RA patients' inflammation storm to achieve clinical remission as soon as possible.

The principle of immune adsorption is the use of highly specific antigen-antibody, or have distinct physical and chemical affinity substances (ligand) and adsorption materials (carrier) made with the adsorbent (column), selective or particular to clean the blood of abundant molecule immunoglobulin and inflammatory factors such as pathogenic factor, to purify the blood and alleviate the condition. It is reported that immunosorbent was first used in the treatment of rheumatoid arthritis in 1994. The related research of immunoadsorption therapy for RA was first published in 1999. Since then, there have been related articles published, all of them showed that the use of immune adsorption treatment of RA patients is positive.[21] The Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis in China in

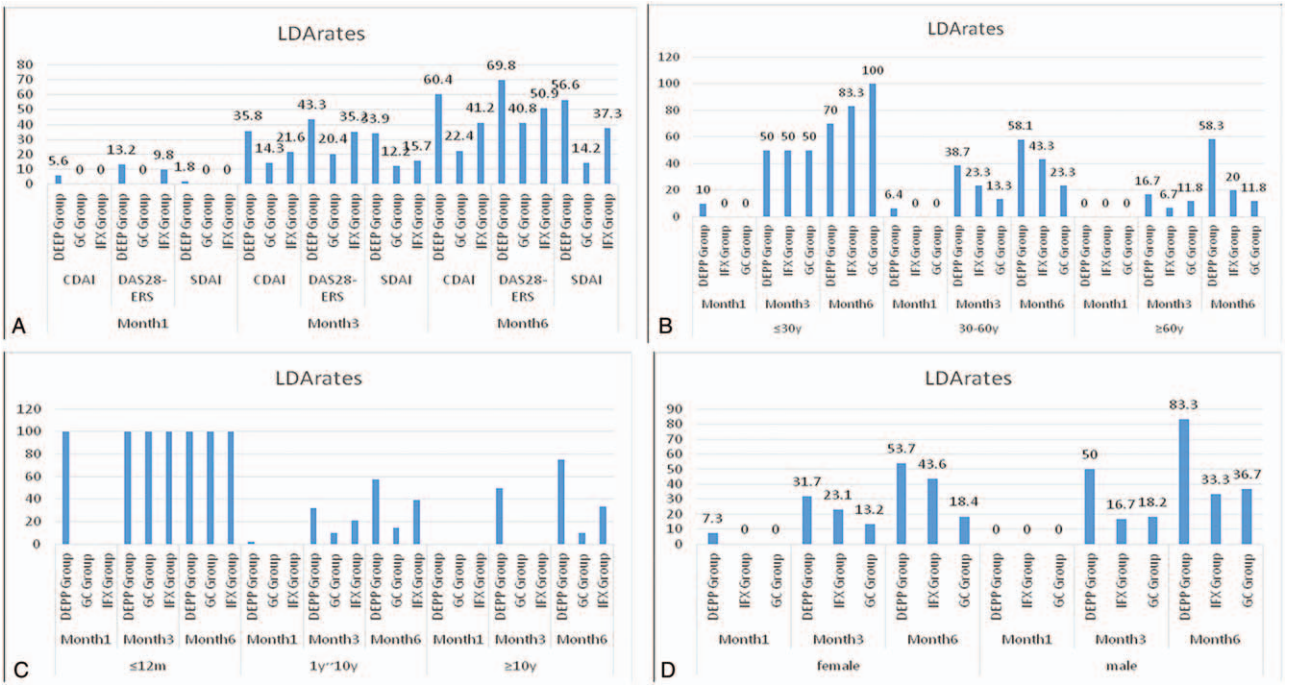

Figure 1. The REM and LDA rates of DFPP treatment were higher than those of the other 2 groups at M1, M3, M6 (A). Patients were grouped according to age, gender, and course of disease. The younger the patients, the higher the rates of REM and LAD of 3 different treatments (B). The shorter the course of the disease, the higher the rates of REM and LAD of 3 different treatments (C). The REM and LAD rates of Male patients were higher than those of female patients of 3 different treatments (D). DFPP = dual filtration plasmapheresis, GC = glucocorticoid, IFX = infliximab, LDA = low disease activity, REM = remission.

2010 pointed out that for patients with high titers of autoantibodies and immunoglobulins, which were ineffective in traditional treatment, immunopurification methods such as plasma exchange and immunoadsorption could be used to treat rheumatoid arthritis.[22]

The purpose of this study is to find a more effective treatment plan for active refractory patients who had a poor response to conventional treatment. At present, biological agents are more and more widely used, so it is necessary to study the efficacy and safety of DFPP combined with a biological agent in the treatment of active refractory RA.

The results showed that the baseline age, sex, course of the disease, and disease activity was similar in the patients from the 3 groups. The results of this study show that compared with the IFX and GC group, the treatment effect of the DFPP group was more rapid, and the remission rate of CDAI (SDAI) in the DFPP treatment group was 35.8% (33.9%), which was significantly higher than that of the IFX and GC group after the treatment of 3 months. When treated for 6 months, the remission rate of DFPP treatment group was over 50%, while in IFX and GC group the percentage of CDAI (SDAI) remission were 41.2% (37.3%) and 22.4% (14.2%). As we all know, it is hard for the RA patient of a long course of the disease to reach REM, especially active refractory RA. This study also showed DFPP treatment has excellent safety which has been confirmed by previous studies.

In summary, the results of this study indicate that DFPP combined with IFX therapy can make the patients with active refractory RA achieve remission more quickly than IFX or GC combined with DMARDs. The remission rate of patients is more prominent at 6 months. DFPP combined with IFX can be widely used as a treatment of refractory active RA.

Limited by the sample size and observation time, the adverse reactions of DFPP did not fully appear. Randomized Controlled Trial with longer observation time should be conducted to observe the long-term efficacy and safety of dual filtration plasmapheresis combined with biological agents in the treatment of active refractory rheumatoid arthritis.

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