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RECEIVED 18 March 2023 ACCEPTED 21 August 2023 PUBLISHED 07 December 2023

#### CITATION

Zeng L, He Q, Deng Y, Li Y, Chen J, Yang K, Luo Y, Ge A, Zhu X, Long Z and Sun L (2023), Efficacy and safety of iguratimod in the treatment of rheumatic and autoimmune diseases: a metaanalysis and systematic review of 84 randomized controlled trials. *Front. Pharmacol.* 14:1189142. doi: 10.3389/fphar.2023.1189142

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# Efficacy and safety of iguratimod in the treatment of rheumatic and autoimmune diseases: a meta-analysis and systematic review of 84 randomized controlled trials

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# **Objective:** To evaluate efficacy and safety of iguratimod (IGU) in the treatment of rheumatic and autoimmune diseases.

**Methods:** Databases such as Pubmed, Embase, Sinomed were searched (as of July 2022) to collect randomized controlled trials (RCTs) of IGU in the treatment of rheumatic and autoimmune diseases. Two researchers independently screened the literature, extracted data, assessed the risk of bias of the included literature, and performed meta-analysis using RevMan 5.4 software.

**Results:** A total of 84 RCTs and 4 types of rheumatic and autoimmune diseases [rheumatoid arthritis (RA), ankylosing spondylitis (AS), primary Sjögren's syndrome (PSS) and Autoimmune disease with interstitial pneumonia]. Forty-three RCTs reported RA and showed that IGU + MTX therapy can improve ACR20 (RR 1.45 [1.14, 1.84], p = 0.003), ACR50 (RR 1.80 [1.43, 2.26], p < 0.0000), ACR70 (RR 1.84 [1.27, 2.67], p = 0.001), DAS28 (WMD -1.11 [-1.69, -0.52], p = 0.0002), reduce ESR (WMD -11.05 [-14.58, -7.51], p < 0.00001), CRP (SMD -1.52 [-2.02, -1.02], p < 0.00001), RF (SMD -1.65 [-2.48, -0.82], p < 0.0001), and have a lower incidence of adverse events (RR 0.84 [0.78, 0.91], p < 0.00001) than the control group. Nine RCTs reported AS and showed that IGU can decrease the BASDAI score (SMD -1.62 [-2.20, -1.05], p < 0.00001), BASFI score (WMD -1.07 [-1.39, -0.75], p < 0.00001), VAS (WMD -2.01 [-2.83, -1.19], p < 0.00001), inflammation levels (decreasing ESR, CRP and TNF-a). Thirty-two RCTs reported PSS and showed that IGU can reduce the ESSPRI score (IGU + other therapy group: WMD -1.71 [-2.44, -0.98], p < 0.00001; IGU only group: WMD -2.10 [-2.40, -1.81], p < 0.00001) and ESSDAI score (IGU + other therapy group: WMD -1.62 [-2.30, -0.94], p < 0.00001; IGU only group:

WMD –1.51 [–1.65, –1.37], p < 0.00001, inhibit the inflammation factors (reduce ESR, CRP and RF) and increase Schirmer's test score (IGU + other therapy group: WMD 2.18 [1.76, 2.59], p < 0.00001; IGU only group: WMD 1.55 [0.35, 2.75], p = 0.01); The incidence of adverse events in IGU group was also lower than that in control group (IGU only group: RR 0.66 [0.48, 0.98], p = 0.01). Three RCTs reported Autoimmune disease with interstitial pneumonia and showed that IGU may improve lung function.

**Conclusion:** Based on current evidence, IGU may be a safe and effective therapy for RA, AS, PSS and autoimmune diseases with interstitial pneumonia.

Systematic Review Registration: (CRD42021289489).

#### KEYWORDS

autoimmune disease, iguratimod, rheumatoid arthritis, ankylosing spondylitis, primary Sjögren's syndrome, autoimmune disease with interstitial pneumonia, systematic review, meta-analysis

# **1** Introduction

The pathogenesis of rheumatic immune diseases is complex, and it is an inflammatory disease that may lead to impaired immune system due to various reasons (involving the musculoskeletal system, joints and their surrounding soft tissues, etc.) (Konig, 2020; Adelowo et al., 2021). In recent years, the prevalence of rheumatic immune diseases has been on the rise (Hyrich and Machado, 2021), among which rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) are more common and have certain disability (Charoenngam, 2021) ]. Meanwhile, with the progression of the disease, most patients may develop complications such as kidney, iris, skin, heart and other organ damage (van der Woude and van der Helm-van Mil, 2018; Dai et al., 2021). Especially in active disease, there may be radioactive progression, and severe cases may lead to joint deformity and even loss of self-care function in life (Otón and Carmona, 2019). Therefore, rheumatic immune diseases with high disease activity will generate a great economic burden for both society and patients (Otón and Carmona, 2019). The current treatments for rheumatic diseases and autoimmune diseases are precision medicine based on drugs (Aletaha, 2020; Radu and Bungau, 2021), with the aim of controlling the progression of inflammation and reducing inflammatory damage (Winthrop, 2017; Aletaha and Smolen, 2018). It mainly includes traditional synthetic DMARDs, biologics DMARDs and synthetic targeted DMARDs (Goodman, 2015). Among them, biological DMARDs can be divided into two categories: biological agents (bDMARDs) and synthetic targeted (tsDMARDs) (Akram et al., 2021). bDMARDs include the tumor necrosis factor inhibitor class of adalimumab, infliximab, etanercept, and the IL-6 antagonist tocilizumab. tsDMARDs include the Janus kinase (JAK) inhibitor tofacitinib (Winthrop, 2017). Although the efficacy of the above drugs has been proven, their high prices make it impossible for patients in developing countries, including China, to benefit (Drosos et al., 2020). Studies have shown that patients in developed countries are also becoming increasingly prominent due to poor compliance and high recurrence rates related to medication problems (Tanaka, 2016; Ghabri et al., 2020). Traditional DMARDs are widely used in clinic because of their acceptable side effects and reasonable price. For example, methotrexate (MTX) is the most widely used DMARDs for the treatment of RA (Wang W. et al., 2018). Because of its effectiveness, acceptable side effects, and reasonable price, ACR recommends it as the first-choice drug in the initial treatment regimen for RA patients (Cronstein and Aune, 2020). However, there are still about 30%–40% of patients who are insensitive to MTX treatment, have poor treatment effect, or fail to benefit from it because of side effects (Cronstein and Aune, 2020). Strand et al. reported that the ACR50 of MTX in RA was 46%, and the ACR70 was 23% (Strand et al., 1999). According to multiple clinical trials, the combined use of DMARDs is one of the effective ways to improve the efficacy (Kremer et al., 2002; Ichikawa et al., 2005; Capell et al., 2007).

Iguratimod (IGU) is a new type of small molecule DMARDs developed in Japan. As an immunomodulator, through immunomodulation, it reduces immune response, inhibits collagenous arthritis, and relieves the destruction of bone and cartilage tissue (Li et al., 2013; Mizutani et al., 2021). IGU can also inhibit the activity of nuclear factors, thereby inhibiting the production of inflammatory cytokines, IL-1, IL-6, IL-8, and TNF, and inhibiting the production of immunoglobulins to exert anti-inflammatory, antiimmune, and anti-inflammatory effects. (Li et al., 2013; Xie S. et al., 2020). Several studies have shown that IGU has good efficacy in rheumatic diseases and autoimmune diseases, such as improving RA, AS, systemic lupus erythematosus, IG4-RD, pulmonary interstitial disease, primary Sjögren's syndrome (PSS), etc. (Harjacek, 2021; Pu et al., 2021; Zeng et al., 2022a). In clinical practice, more and more rheumatologists use IGU to treat rheumatic and autoimmune diseases, but its efficacy and safety are still uncertain. Therefore, we collected randomized controlled trials (RCTs) of IGU in the treatment of rheumatic and autoimmune diseases in order to conduct a systematic review and meta-analysis of its efficacy and safety.

# 2 Materials and methods

# 2.1 Protocol

This systematic review and meta-analysis were conducted strictly in accordance with the protocol registered in PROSPERO (CRD42021289489) and PRISMA-guidelines (see Supplementary Materials) (Page et al., 2021).



# 2.2 Search criteria

# 2.2.1 Study design

All RCTs on IGU for rheumatic and autoimmune diseases were included. There are no restrictions on publication year, publication language, publication journal, *etc.* 

# 2.2.2 Participants

Patients were diagnosed with any rheumatic and autoimmune diseases by accepted criteria.

# 2.2.3 Intervention methods

The experimental group was treated with IGU, which was administered orally. The course of treatment and the dose were

not limited, and it could be combined or not combined with other therapies. The control group is therapy that does not contain IGU, including but not limited to placebo, conventional therapy, *etc.* 

#### 2.2.4 Outcomes

Outcomes are the disease activity indices (such as BASDAI and ACR20), inflammatory factor indicators (such as ESR, CRP, RF) and adverse events.

# 2.2.5 Exclusion criteria

1) Duplicate publications; 2) Unable to obtain full text or incomplete data; 3) Reviews, case reports, animal experiments, *etc.*,; 4) Retracted studies; 5) observational studies.

#### TABLE 1 The characteristics of the included studies.

Disease	Study	Sample s	ize	Intervention		Relevant outcomes	Mean age (years)		Duration
		Trial group	Control group	Trial group	Control group		Trial group	Control group	
RA	Lü et al. (2008)	185	95	a: IGU 25 mg Qd; b: 25 mg Bid	Placebo	American college of rheumatology (ACR)20, ACR50, ACR70, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), adverse events	a: 48.05 ± 10.30; b: 46.98 ± 10.93	47.46 ± 10.30	24 weeks
	Tian and Tao (2017)	58	58	IGU 25 mg Bid + MTX 10 mg once or twice a week	MTX 10 mg once or twice a week	Disease activity score (DAS)28, ESR, CRP, adverse events	52.6 ± 7.6	49.7 ± 8.4	24 weeks
	Qi et al. (2019)	40	40	IGU 25 mg Bid + MTX 7.5 mg once a week at the beginning, gradually increase to 10 mg within 4 weeks	MTX 7.5 mg once a week at the beginning, Gradually increase to 10 mg within 4 weeks	ACR20, ACR50, ACR70, ESR, CRP, adverse events	25-65	24 weeks	
	Ishiguro et al. (2013), Hara et al. (2014)	164	68	IGU 25 mg Qd for the first 4 weeks of the extension period 25 mg Bid for the subsequent 20 weeks + MTX 6-8 mg once a week	MTX 6-8 mg once a week + placebo	ACR20, ACR50, ACR70, CRP, RF, DAS28, adverse events	54.8 ± 9.9	53.5 ± 10.0	24 weeks
	Li et al. (2019a)	51	51	IGU 25 mg Bid + MTX 15 mg once a week	MTX 15 mg once a week	Adverse events	74.16 ± 2.42	74.32 ± 2.52	15 weeks
	Hu (2014)	20	20	IGU 25 mg Bid	MTX 10 mg once a week	DAS28, ACR20, adverse events	47.3 ± 13.5	46.2 ± 15.8	24 weeks
	Du et al. (2008)	326	163	a: IGU 25 mg for the first 4 weeks and 50 mg for the subsequent 20 weeks; b: IGU 25 mg Bid	MTX 10 mg/week for the first 4 weeks and 15 mg/week for the subsequent 20 weeks	ACR20, ACR50, ACR70, ESR, CRP, RF, adverse events	a: 46.0 ± 10.6; b: 45.9 ± 10.4	47.2 ± 11.0	24 weeks
	Lu et al. (2009)	132	64	IGU 25 mg for the first 4 weeks and 50 mg for the subsequent 24 weeks	placebo	CRP, ESR, adverse events	57.5 ± 10.8	57.0 ± 10.8	28 weeks
	Xia et al. (2020)	50	50	IGU 25 mg Bid + MTX 7.5 mg once a week at the beginning, increase by 2.5 mg per week, with a final dose of 15 mg	MTX 7.5 mg once a week at the beginning, increase by 2.5 mg per week, with a final dose of 15 mg + Tripterygium glycosides 1–1.5 mg/kg	ESR, CRP	53.73 ± 2.78	53.62 ± 2.45	12 weeks
	Lu, 2014; Xia et al. (2016)	100	50	a: IGU 25 mg Bid + MTX 10 mg once a week; b: IGU 25 mg Bid	MTX 10 mg once a week	ESR, CRP	46.63 ± 10.61		24 weeks
	Zhao et al. (2016)	60	30	a: IGU 25 mg Bid + MTX 10 mg once a week; b: IGU 25 mg Bid	MTX 15 mg once a week	ACR20, ACR50, ACR70, adverse events	a: 30.1 ± 2.4; b: 29.3 ± 2.7	28.1 ± 3.4	24 weeks
	Shi et al. (2015)	30	30	IGU 25 mg Bid + MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 4 weeks	MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 4 weeks	DAS28, ESR, CRP, ACR20, ACR50, ACR70, adverse events	48.9 ± 12.2	48.4 ± 10.2	24 weeks
	Meng et al. (2015)	33	33	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week + Leflunomide 10 mg Qd	DAS28, ACR20, ACR50, ACR70, adverse events	44.2 ± 20.5	41.7 ± 22.8	16 weeks
	Bi (2019)	30	30	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week + Leflunomide 20 mg Qd	DAS28, adverse events	53.10 ± 12.90	54.60 ± 11.88	12 weeks
	Zhang (2018)	60	60	IGU 25 mg Qd	MTX 10 mg once a week + Leflunomide 20 mg Qd	ACR20, CRP, ESR, RF, adverse events	46.35 ± 18.19		24 weeks
	Li et al. (2016)	44	40	IGU 25 mg Qd + MTX 7.5–10 mg once a week	MTX 7.5–10 mg once a week + Tripterygium glycosides 20 mg Bid	DAS28, ESR, CRP, adverse events	60–77	60-82	12 weeks
	Mo et al. (2018)	30	30	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week + Tripterygium glycosides 20 mg Bid	DAS28, ESR, CRP, CCP, RF, adverse events	45 ± 11.6	43.3 ± 10.25	12 weeks
	Duan et al. (2015)	30	30	IGU 25 mg Bid + MTX 10 mg once a week at the beginning, gradually increase to 12.5 mg within 4 weeks	MTX 10 mg once a week at the beginning, gradually increase to 12.5 mg within 4 weeks	ESR, CRP, DAS28, adverse events	48.9 ± 12.2	48.4 ± 10.2	24 weeks
	Xiong and GengGuanghui (2020)	51	51	IGU 25 mg Bid + MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 2 weeks; 15 mg once a week after 4 weeks	MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 2 weeks; 15 mg once a week after 4 weeks	Adverse events	48.21 ± 6.04	48.33 ± 5.93	24 weeks
	Shang (2014)	20	20	IGU 25 mg Bid	Etoricoxib 60 mg Qd	Adverse events	43.73 ± 3.62	45.73 ± 3.56	12 weeks
	Mo and Ma (2015)	30	30	IGU 25 mg Bid + MTX 15 mg once a week	MTX 15 mg once a week	ACR20, ACR50, ACR70, ESR, CRP, RF, adverse events	31.8 ± 8.5	31.9 ± 8.6	12 weeks
	Tian et al. (2020)	120	120	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week + Leflunomide 20 mg Qd	DAS28, ESR, CRP, RF, adverse events	50 ± 10	49 ± 11	52 weeks

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#### TABLE 1 (Continued) The characteristics of the included studies.

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Disease	Study	Sample s		Intervention		Relevant outcomes	Mean age (years)		Duration
		Trial group	Control group	Trial group	Control group		Trial group	Control group	
	Xu et al. (2015a)	72	38	a: IGU 25 mg Bid + MTX 7.5–20 mg once a week; b: IGU 25 mg Bid	MTX 7.5-20 mg once a week	ESR, CRP, RF, adverse events	a: 46.10 ± 17.09; b: 44.71 ± 9.32	43.28 ± 10.46	48 weeks
	Xu et al. (2017a)	42	41	IGU 25 mg Bid + MTX 7.5-20 mg once a week	MTX 7.5–20 mg once a week	DAS28, ESR, CRP	46.34 ± 2.29	46.19 ± 2.57	48 weeks
	Yan and Wang (2018)	35	35	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	Adverse events	56 ± 7	56 ± 7	24 weeks
	Fan et al. (2020)	38	37	IGU 25 mg Bid + MTX 10 mg once a week at the beginning: 12.5 mg once a week after 2 weeks; 15 mg once a week after 4 weeks	MTX 10 mg once a week at the beginning; 12.5 mg once a week after 2 weeks; 15 mg once a week after 4 weeks	DAS28	49.0 ± 10.1	48.7 ± 10.2	24 weeks
	Meng et al. (2016b)	30	30	IGU 25 mg Bid + MTX 15 mg once a week	MTX 15 mg once a week	DAS28, adverse events	41.6 ± 20.3	45.1 ± 19.2	16 weeks
	Wang et al. (2019a)	47	46	IGU 25 mg Bid + MTX 15 mg once a week	MTX 15 mg once a week	CRP, RF, ESR, DAS28	48.13 ± 6.40	47.83 ± 6.37	24 weeks
	Meng et al. (2017)	60	60	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	RF, CRP, adverse events	64.83 ± 9.41	64.31 ± 8.22	12 weeks
	Ju et al. (2020)	58	58	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	DAS28, ESR, CRP, RF	42.31 ± 13.78	41.87 ± 13.94	24 weeks
	Zhao and Hao (2018)	36	36	IGU 25 mg Bid + MTX 7.5 mg once a week	MTX 7.5 mg once a week	DAS28, CRP, adverse events	47.20 ± 3.40	50.80 ± 4.10	12 weeks
	Li and WH (2020)	20	13	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week + Adalimumab 40 mg once every 2 weeks	DAS28	58 ± 11	55 ± 11	24 weeks
	Xu et al. (2015b)	30	28	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	RF, CRP, ESR, DAS28, adverse events	56 ± 12	51 ± 13	24 weeks
	Chen et al. (2018)	60	60	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	CRP, adverse events	45.7 ± 5.4	45.9 ± 4.8	24 weeks
	Zhao et al. (2017a)	63	33	a: IGU 25 mg Bid; b: IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	ACR20, ACR50, ACR70, DAS28, ESR, CRP, RF, adverse events	a: 46.46 ± 11.01; b: 45.97 ± 10.75	46.31 ± 10.89	24 weeks
	Deng (2017)	59	31	a: IGU 25 mg Bid + MTX 10 mg once a week; b: IGU 25 mg Bid	MTX 10 mg once a week + Leflunomide 20 mg Qd	DAS28, ESR, CRP, RF, adverse events	47.23 ± 15.62		48 weeks
	Xie et al. (2018)	39	39	IGU 25 mg Bid + MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 2 weeks; 15 mg once a week after 4 weeks	MTX 10 mg once a week at the beginning; 12.5 mg twice a week after 2 weeks; 15 mg once a week after 4 weeks	DAS28, adverse events	62.89 ± 4.57	62.74 ± 3.96	16 weeks
	Rao et al. (2014)	60	30	a: IGU 25 mg Bid; b: IGU 25 mg Qd	MTX 10 mg once a week	ACR20, ACR50, ACR70	42.6 ± 5.2	1	12 weeks
	Wang et al. (2022)	60	60	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	CRP, adverse events	54 ± 14	55 ± 13	12 weeks
	Dai et al. (2022)	60	60	IGU 25 mg Bid + MTX 7.5 mg once a week	MTX 7.5 mg once a week	DAS28, CRP, ESR, RF	59.4 ± 7.8	60.1 ± 9.7	12 weeks
	Sun and Li (2022)	43	43	IGU 25 mg Bid + MTX 10 mg once a week	MTX 10 mg once a week	Adverse events	49.05 ± 4.32	48.96 ± 5.24	24 weeks
	Wu et al. (2022)	58	58	IGU 25 mg Bid + MTX 10 mg once a week + Tripterygium wilfordii polyglycosides 50 mg for the first time and 20 mg Qd after 3days	MTX 10 mg once a week + Tripterygium wilfordii polyglycosides 50 mg for the first time and 20 mg Qd after 3days	DAS28, CRP, ESR, RF	61.48 ± 4.36	62.73 ± 4.58	18 weeks
	DongZhang et al. (2019)	52	104	IGU 25 mg Bid + Tripterygium glycosides 1.5 mg/(kg-d)	a: Prednisone + Sulfasalazine; b: Tripterygium glycosides 1.5 mg/(kg·d)	Forced vital capacity (FVC), Forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), CRP, RF, adverse events	54.7 ± 5.1	a: 55.6 ± 4.9; b: 54.1 ± 5.4	24 weeks
AS	Qiu et al. (2016)	18	18	Iguratimod 25 mg Bid	NSAIDs + DMARDs	ESR, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), visual analogue scale (VAS), back pain score, adverse events	37.3 ± 7.0	34.5 ± 9.3	24 weeks
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#### TABLE 1 (Continued) The characteristics of the included studies.

Disease	Study	Sample s		Intervention		Relevant outcomes	Mean age (years)		Duration
		Trial group	Control group	Trial group	Control group		Trial group	Control group	
	Yuan et al. (2020)	41	39	Iguratimod 25 mg Bid + Etoricoxib tablets 60 mg Qd. + ibuprofen 300 mg Tid. + methotrexate 15 mg once a week	Etoricoxib tablets 60 mg Qd. + ibuprofen 300 mg Tid. + methotrexate 15 mg once a week	VAS, CRP, ESR, adverse events	39.28 ± 5.30	40.08 ± 5.67	12 weeks
	Pang et al. (2020)	39	39	Iguratimod 25 mg Bid + Etanercept 25 mg tiwce a week	Etanercept 25 mg tiwce a week	ESR, CRP, BASDAI	24.85 ± 4.18	25.01 ± 4.29	12 weeks
	Lin et al. (2019)	24	24	Iguratimod 25 mg Bid + Sulfasalazine 1 g Bid. + methotrexate 10 mg once a week + NSAIDs	Sulfasalazine 1 g Bid. + methotrexate 10 mg once a week + NSAIDs	BASDAI, BASFI, VAS, adverse events	32.71 ± 8.80	28.21 ± 6.69	24 weeks
	Xu et al. (2019)	21	21	Iguratimod 25 mg Bid + Celecoxib 0.2 g Qd	Sulfasalazine 1 g Bid. + Celecoxib 0.2 g Qd	BASDAI, BASFI, VAS, ESR, CRP, adverse events	35.1 ± 10.3	34.3 ± 9.5	24 weeks
	Zeng et al. (2016)	25	25	Iguratimod 25 mg Bid + Meloxicam 7.5 mg Qd	guratimod 25 mg Bid + Meloxicam 7.5 mg Qd Sulfasalazine 0.75 g Tid. + Meloxicam 7.5 mg Qd BASDAI, CRP, adverse events				
	Li et al. (2021a)	48	25	Iguratimod 50 mg Qd + NSAIDs	NSAIDs + Placebo	BASDAI, BASFI, CRP, ESR, adverse events	31.38 ± 7.36	30.28 ± 5.94	24 weeks
	Li et al. (2021b) 30 30		Iguratimod 25 mg Bid + Sulfasalazine 1 g Bid + Celecoxib 200 mg Bid	Sulfasalazine 1 g Bid + Celecoxib 200 mg Bid	BASDAI, VAS, CRP, ESR, adverse events	28.52 ± 9.43	27.87 ± 8.05	12 weeks	
			Iguratimod 25 mg Bid + Sulfasalazine 0.5-1 g Bid + Thalidomide 50-200 mg Qn	Sulfasalazine 0.5–1 g Bid + Thalidomide 50–200 mg Qn	BASDAI	31.24 ± 4.71	30.01 ± 4.68	24 weeks	
PS	Gu (2020)	40	40	Iguratimod 25 mg Bid	Prednisone 8 mg Qd + HCQ 200 mg Bid	RF, Adverse events	66.72 ± 4.34	66.51 ± 4.23	12 weeks
	Jiang et al. (2014)	25	25	Iguratimod 25 mg Bid	Prednisone 5-10 mg Qd + HCQ 200 mg Bid + Bromoethylsine 16 mg Bid	EULAR SS Patient Reported Index (ESSPRI), EULAR SS disease activity index (ESSDAI), Schirmer's test, Adverse events	29.3 ± 9.7	32.5 ± 11.5	12 weeks
	Zhao (2019)	41	41	Iguratimod 25 mg Bid	Prednisone 8 mg Qd + HCQ 200 mg Bid	RF, ESR, Adverse events	55.51 ± 6.52	54.52 ± 6.54	12 weeks
	Lu and Zhang (2021)	48	48	Iguratimod 25 mg Bid + HCQ 0.2 g Bid	HCQ 0.2 g Bid	ESR, RF, adverse events	45.52 ± 7.48	44.24 ± 8.32	12 weeks
	Li et al. (2020)	23	23	Iguratimod 25 mg Bid	Prednisone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, ESR, Adverse events	46.29 ± 1.24	46.38 ± 1.37	12 weeks
	Zhang (2019)	60	60	Iguratimod 25 mg Bid + Methylprednisolone 8 mg	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, ESSDAI, Schirmer's test	49.43 ± 3.74		12 weeks
	Jia (2020)	43	43	Iguratimod 25 mg Bid	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, ESSDAI, ESR, RF, adverse events	50.47 ± 9.11	50.47 ± 9.11	16 weeks
	Yu (2020)	38	38	Iguratimod 25 mg Bid	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESR, RF	41.18 ± 3.36	41.14 ± 3.39	12 weeks
	Shao et al. (2020)	44	22	Iguratimod 25 mg Bid	Placebo	ESSPRI, ESR, ESSDAI, Adverse events	49.5 ± 12.3	48.2 ± 11.5	24 weeks
	Chen et al. (2022)	62	62	Iguratimod 25 mg Bid + Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	ESSPRI, ESSDAI, ESR, RF	68.02 ± 3.02	68.50 ± 3.05	12 weeks
	Donghui (2019)	30	30	Iguratimod 25 mg Bid + Methylprednisolone 8 mg	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESR, adverse events	46.9 ± 4.2	46.5 ± 4.3	12 weeks
	Zhang and Shen (2019)	43	43	Iguratimod 25 mg Bid + Methylprednisolone 8 mg	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, ESSDAI, ESR, RF, Schirmer's test, adverse events	40.35 ± 9.41	41.03 ± 10.01	12 weeks
	Jiang et al. (2016)	30	30	Iguratimod 50 mg Qd	Prednisone 8 mg Qd + HCQ 200 mg Bid	RF, ESR, Adverse events	45.13 ± 12.11	46.33 ± 13.74	12 weeks
	Xie et al. (2020b)	38	38	Iguratimod 25 mg Bid + Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	ESR, CRP, Schirmer's test, Adverse events	57.3 ± 7.92	56.8 ± 8.44	24 weeks
	Jiang et al. (2020)	25	25	Iguratimod 50 mg Qd	Prednisone 10 mg, hydroxychloroquine (HCQ) 400 mg, new hydrochloride bromine ethyl Qd	EULAR Sjögren's syndrome patient-reported index (ESSPRI), ESSDAI, Schirmer's test, Adverse events	29.3 ± 9.7	32.5 ± 11.5	12 weeks
	Bai and Jiao (2019)	30	30	Iguratimod 25 mg Bid	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid + Leflunomide 50 mg Qd	ESSPRI, ESSDAI, RF, ESR, Adverse events	43 ± 21	43 ± 10	12 weeks

10.3389/fphar.2023.1189142

#### TABLE 1 (Continued) The characteristics of the included studies.

Sample							
	size	Intervention		Relevant outcomes	Mean age (years)		Duration
Trial group	Control group	Trial group	Control group		Trial group	Control group	
43	43	Iguratimod 25 mg Bid	Methylprednisolone 4 mg Qd + HCQ 200 mg Bid	Schirmer's test, ESR, RF	51.8 ± 10.3	50.1 ± 9.9	12 weeks
20	20	Iguratimod 25 mg Bid + HCQ 100 mg Bid + Prednisone 5 mg Bid	HCQ 100 mg Bid + Prednisone 5 mg Bid	ESSPRI, ESSDAI, ESR, RF, Schirmer's test, adverse events	66.15 ± 3.71	66.31 ± 3.98	12 weeks
47	47	Iguratimod 25 mg Bid Prednisone 8 mg Qd + HCQ 200 mg Bid ESSPRI, ESSDAI, ESR, RF, Schirmer's test		ESSPRI, ESSDAI, ESR, RF, Schirmer's test	44.5 ± 13.2	45.3 ± 13.1	12 weeks
100	100	Iguratimod 25 mg Bid	Prednisone + HCQ + olfaction	FVC, maximum mid-expiratory flow (MMF), ESR, adverse events	30.68 ± 3.51	31.00 ± 3.60	20 weeks
Luo et al. (2018b) 40 40		Iguratimod 25 mg Bid	ESR, RF, adverse events	43.6 ± 10.5	45.2 ± 12.9	12 weeks	
32	32	Iguratimod 25 mg Bid + Total Glucosides of Paeony 0.6 g Bid + HCQ 0.1 g Bid	Total Glucosides of Paeony 0.6 g Bid + HCQ 0.1 g Bid	ESSPRI, ESSDAI, Schirmer's test, ESR, RF, Adverse events	66.8 ± 7.7	65.3 ± 8.2	12 weeks
25	25	Iguratimod 25 mg Bid + Basic therapy	HCQ 200 mg Bid + Basic therapy	ESR, RF, adverse events	45.3 ± 2.8	45.7 ± 2.8	Unkown
30	30	Iguratimod 25 mg Bid + Methylprednisolone 8 mg	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESSDAI, ESSPRI, ESR, CRP, adverse events	45.16 ± 6.37	40.15 ± 6.65	16 weeks
34	34	Iguratimod 25 mg Bid	Prednisone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, RF, ESR, Adverse events	40.05 ± 3.16	40.02 ± 3.15	12 weeks
24	22	Iguratimod 25 mg Bid + Chere Cunjing Granules	Chere Cunjing Granules (Traditional Chinese Medicine)	ESSPRI, ESSDAI, ESR, CRP, adverse events	45.95 ± 11.52	48.92 ± 11.53	12 weeks
20	20	Iguratimod 25 mg Bid + Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	Total Glucosides of Paeony 0.6 g Tid + HCQ 0.2 g Bid	ESR, CRP, Adverse events	56.87 ± 2.56	56.23 ± 2.86	12 weeks
34	34	Iguratimod 25 mg Bid + Methylprednisolone 8 mg	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESR, RF	36.48 ± 1.25	36.51 ± 1.19	12 weeks
50	50	Iguratimod 25 mg Bid + Methylprednisolone	HCQ 200 mg Bid + Methylprednisolone	ESR, RF	42.13 ± 9.97	42.08 ± 9.65	12 weeks
42	42	Iguratimod 25 mg Bid	Methylprednisolone 8 mg Qd + HCQ 200 mg Bid	ESSPRI, adverse events	40.97 ± 10.24	41.56 ± 10.21	2 weeks
40	40	Iguratimod 25 mg Bid + Total Glucosides of Paeony 0.6 g Tid + HCQ 200 mg Bid + methylprednisolone 8 mg Qd	Total Glucosides of Paeony 0.6 g Tid + HCQ 200 mg Bid + methylprednisolone 8 mg Qd	ESSDAI, ESSPRI, ESR, RF, adverse events	44.05 ± 8.82	43.68 ± 8.75	12 weeks
nuang et al. (2021) 10 10 Iguratimod 25 mg Bid + Prednisone 5-10 mg Tid			Cyclophosphamide + Prednisone 5–10 mg Tid	Dispersive carbon monoxide (DLCO), 6-min walk test (6MWT), CRP, ESR, RF, adverse events	45.69 ± 2.80	45.31 ± 2.78	24 weeks
	group           43           20           47           100           40           25           30           24           20           34           20           34           20           34           20           34           20           34           20           34           20           34           42           40	group         group           43         43           20         20           47         47           100         100           40         40           20         32           21         25           22         25           30         30           24         22           25         20           34         34           24         22           25         50           24         22           25         50           24         22           25         34           24         22           25         50           26         34           27         20           28         24           29         20           20         34           34         34           35         50           36         50           37         42           40         40	groupgroup4343Iguratimod 25 mg Bid2020Iguratimod 25 mg Bid + HCQ 100 mg Bid + Prednisone 5 mg Bid4747Iguratimod 25 mg Bid4747Iguratimod 25 mg Bid100100Iguratimod 25 mg Bid4040Iguratimod 25 mg Bid503232Iguratimod 25 mg Bid + Total Glucosides of Pacony 0.6 g Bid + HCQ 0.1 g Bid503030Iguratimod 25 mg Bid + Basic therapy3030Iguratimod 25 mg Bid + Methylprednisolone 8 mg3434Iguratimod 25 mg Bid + Chere Cunjing Granules2020Iguratimod 25 mg Bid + Total Glucosides of Pacony 0.6 g Tid + HCQ 0.2 g Bid3434Iguratimod 25 mg Bid + Methylprednisolone 8 mg5050Iguratimod 25 mg Bid + Methylprednisolone 8 mg5050Iguratimod 25 mg Bid + Methylprednisolone 8 mg4242Iguratimod 25 mg Bid + Total Glucosides of Pacony 0.6 g Tid + HCQ 0.2 g Bid4040Iguratimod 25 mg Bid + Methylprednisolone 8 mg414242Iguratimod 25 mg Bid + Methylprednisolone 8 mg4242Iguratimod 25 mg Bid + Methylprednisolone 8 mg4040Iguratimod 25 mg Bid + Methylprednisolone 8 mg Ad	groupgroupgroup4343Iguratimod 25 mg BidMethylprednisolone 4 mg Q4 + HCQ 200 mg Bid2020Iguratimod 25 mg Bid + HCQ 100 mg Bid + PrednisoneHCQ 100 mg Bid + Prednisone 5 mg Bid4747Iguratimod 25 mg BidPrednisone 8 mg Q4 + HCQ 200 mg Bid100100Iguratimod 25 mg BidPrednisone 8 mg Q4 + HCQ 200 mg Bid4040Iguratimod 25 mg BidPrednisone 8 mg Q4 + HCQ 200 mg Bid525Iguratimod 25 mg BidPrednisone 9 mg Q4 + HCQ 200 mg Bid525Iguratimod 25 mg Bid + Total Glucosides of Pacony 0.6 gTotal Glucosides of Pacony 0.6 g Bid + HCQ 0.1 g Bid5030Iguratimod 25 mg Bid + Methylprednisolone 8 mgMethylprednisolone 8 mg Q4 + HCQ 200 mg Bid3434Iguratimod 25 mg Bid + Chere Cunjing GranulesChere Cunjing Granules (Traditional Chinese Medicine)2020Iguratimod 25 mg Bid + Chere Cunjing GranulesChere Cunjing Granules (Traditional Chinese Medicine)2422Iguratimod 25 mg Bid + Methylprednisolone 8 mgTotal Glucosides of Pacony 0.6 g Tid + HCQ 0.2 g Bid3434Iguratimod 25 mg Bid + Methylprednisolone 8 mgMethylprednisolone 8 mg Q4 + HCQ 200 mg Bid3434Iguratimod 25 mg Bid + Methylprednisolone 8 mgMethylprednisolone 8 mg Q4 + HCQ 200 mg Bid3434Iguratimod 25 mg Bid + Methylprednisolone 8 mgMethylprednisolone 8 mg Q4 + HCQ 200 mg Bid3434Iguratimod 25 mg Bid + Methylprednisolone 8 mgMethylprednisolone 8 mg Q4 + HCQ 200 mg Bid3434Igurati	groupgroupgroupread4343Iguratimed 25 mg BidMethylprednisolone 4 mg Q4 + HQQ 200 mg BidSchirmer's test, ESR, RF2020Iguratimed 25 mg Bid + HQQ 100 mg Bid + Prednisone 5 mg BidESSPRI, ESSDAI, ESR, RF, Schirmer's test, adverse events4747Iguratimed 25 mg BidPrednisone 8 mg Q4 + HQQ 200 mg BidESSPRI, ESSDAI, ESR, RF, Schirmer's test40100Iguratimed 25 mg BidPrednisone 4 mg Q4 + HQQ 200 mg BidESSPRI, ESSDAI, ESR, RF, Schirmer's test4040Iguratimed 25 mg BidPrednisone 4 mg Q4 + HQQ 200 mg BidESS, RF, adverse events4140Iguratimed 25 mg BidPrednisone 8 mg Q4 + HQQ 200 mg BidESS, RF, adverse events4240Iguratimed 25 mg BidPrednisoids of Pacony 0.6 g Bid + HQQ 10 g BidESSPRI, ESSDAI, ESSR, RF, adverse events4332Iguratimed 25 mg Bid + Basic therapyHCQ 200 mg Bid + Basic therapyESSR, RF, adverse events4434Iguratimed 25 mg Bid + Methylprednisolone 8 mg Q4 + HQQ 200 mg BidESSPRI, ESSR, Adverse events4534Iguratimed 25 mg Bid + Chec Cunjing GranulesChere Cunjing Granules (Traditional Chinese Mgdicine)ESSR, RF, Adverse events4534Iguratimed 25 mg Bid + Methylprednisolone 8 mg Q4 + HQQ 200 mg BidESSR, RF, RF, Adverse events4634Iguratimed 25 mg Bid + Methylprednisolone 8 mg Q4 + HQQ 200 mg BidESSRAI, ESSR, RF, Adverse events4734Iguratimed 25 mg Bid + Methylprednisolone 8 mg Q4 + HQQ 200 mg BidESSRAI, ESSR, RF, Adverse events48	Image: Figure	First         Control group         Control group         Control group         First group         Control group           1         4.0         4.0         Igranimod 25 m glid         Methylprednisone 4 m Qd + HCQ 200 m glid         Skinmer's test, SSR, RF         51.8 ± 1.00         51.8 ± 1.00           1         9.0         20.0         Sgranimod 25 m glid + HCQ 100 m glid + Prednisone 7 m glid         SSPRJL ESDAJ, ISSR, RF, Schimmer's test, advence events         64.15 ± 3.01         63.1 ± 3.08           1         0.0         100         Iguratimod 25 m glid + TOOL 100 mg Bid + Prednisone 7 mg Ad + HCQ 200 mg Bid         SSPRJL ESDAJ, ISSR, RF, Schimmer's test, advence events         64.6 ± 3.0



# 2.3 Search strategy

Pubmed, Wanfang Database, Web of Science, China National Knowledge Infrastructure (CNKI), Sinomed, VIP Database, Medline Complete, Embase were searched for literature on IGU for the treatment of rheumatic and autoimmune diseases. The retrieval time is from inception to 1 July 2022. We also searched ClinicalTrials.gov and Cochrane Library. The search strategy was shown in Supplementary Table S1.

# 2.4 Data collection and analysis

#### 2.4.1 Literature screening and data extraction

Two researchers independently screened the title and abstract of the articles revealed from the search. Then, they screened the full text of the relevant articles based on search criteria. Finally, the two researchers reconciled the results and negotiated inconsistencies through discussions with all researchers (Deeks et al., 2020a). Then two researchers independently extracted the basic information, medication regimen, course of treatment, and outcome indicators of eligible RCTs. For inconsistencies, the solution is the same as before.

#### 2.4.2 Quality assessments

The risk of bias assessment of the included trials was independently performed by two investigators. The Cochrane Collaboration's tool was used for assessing risk of bias (Deeks et al., 2020b). The content of the evaluation mainly includes: 1) Whether the method of random allocation is described; 2) Whether the allocation concealment is sufficient; 3) Whether the blind method is used; 4) Whether the withdrawal from the experiment and the loss to follow-up are completely described; 5) Whether the outcome indicators are selectively reported; 6) Whether there are other factors that may affect the quality of the trial. According to the Cochrane Handbook, the above items were judged as "Yes" (low risk of bias), "No" (high risk of bias), and "Unclear" (unclear risk of bias) (Deeks et al., 2020b).

# 2.5 Statistical analysis

Revman 5.4 software were utilized for meta-analysis (Deeks et al., 2020c). For dichotomous variables data, use the risk ratio (RR). For continuous variables data, when the results of different experiments are expressed in the same unit of measurement, the weighted mean difference (WMD) is used; when the results of the experiments are expressed in different units of measurement, the standard mean difference (SMD) is used. Effect sizes were expressed as 95% confidence intervals (CI). To analyze the heterogeneity between results, the chi-square test was employed. If heterogeneity was deemed small (p > 0.1, I2<50%), the fixedeffects model was utilized for analysis. Otherwise, the randomeffects model was used. STATA 15 was used to detect publication bias with the Egger method (for continuous variables) and Harbord methods (for dichotomous variables) for outcomes with RCTs  $\geq$ 4. p > 0.1 is considered indicative of no publication bias. The level of evidence of efficacy indicators (such as ACR and BASFI) and adverse events was evaluated by the GRADE tool (GRADEpro, 2015), following the GRADE handbook (Schünemann et al., 2013).



# **3** Results

#### 3.1 Literature search results

A total of 1,698 preliminary related literature were detected in this study, and a total of 1,594 literature that did not conform to the research type and content were excluded. After the primary screening, 104 records were obtained. According to the inclusion and exclusion criteria and the completeness of the literature information, 18 records were excluded from the second screening after reading the full text (GuifengLi, 2014; He et al., 2015; Okamura et al., 2015; Meng et al., 2016a; Lin, 2016; Yoshioka et al., 2016; Zhu et al., 2016; Wang, 2017; Wang et al., 2017; Luo Y. et al., 2018; Wang X. et al., 2018; Huang and Ma, 2018; Luo et al., 2019; Shang et al., 2019; Suto et al., 2019; Gu et al., 2020; ManXie, 2020; Xu et al., 2021), and 86 records [(GuifengLi, 2014; Lü et al., 2008; Tian and Tao, 2017; Qi et al., 2019; Hara et al., 2014; Ishiguro et al., 2013; Li L. et al., 2019; Hu, 2014; Xia et al., 2020; Xia et al., 2016; Lu, 2014; Zhao et al., 2016; Shi et al., 2015; Meng et al., 2015; Bi, 2019; Zhang, 2018; Li et al., 2016; Mo et al., 2018; Duan et al., 2015; Xiong and GengGuanghui, 2020; Shang, 2014; Mo and Ma, 2015; Tian et al., 2020; Xu B. et al., 2015; Xu LM. et al., 2017; Yan and Wang, 2018; Fan et al., 2020; Meng et al., 2016b; Wang L. et al., 2019; Meng et al., 2017; Ju et al., 2020; Zhao and Hao, 2018; Li and WH, 2020; Xu YM. et al., 2015; Chen et al., 2018; Zhao et al., 2017a; Deng, 2017; Xie et al., 2018; Rao et al., 2014; Wang et al., 2022; Dai et al., 2022; Sun and Li, 2022; Wu et al., 2022; Dong Zhang et al., 2019; Qiu et al., 2016; Yuan et al., 2020; Pang et al., 2020; Lin et al., 2019; Xu et al., 2019; Zeng et al., 2016; Li Y. et al., 2021; Bai et al., 2021; Li X. et al., 2021; Gu, 2020; Jiang et al., 2014; Zhao, 2019; Lu and Zhang, 2021; Li et al., 2020; Zhang, 2019; Jia, 2020; Yu, 2020; Shao et al., 2020; Chen et al., 2022; Donghui, 2019; Zhang and Shen, 2019; Jiang et al., 2016; Xie H. et al., 2020; Jiang et al., 2020; Bai and Jiao, 2019; Rao et al., 2022; Ding et al., 2022; Xu D. et al., 2017; Zhang et al., 2019; Luo Q. et al., 2018; Wang Y. et al., 2019; Zhao, 2020; Liang et al., 2021; Li et al., 2018; Jiang, 2021; Yi, 2018; Zhuang, 2020; Xia et al., 2017; Gu, 2022; Liu, 2022; Zhuang et al., 2021; Du et al., 2008; Lu et al., 2009) were finally included in the quantitative and qualitative analysis of the review. The literature screening process and results are shown in Figure 1.

# 3.2 Description of included trials

Two records (Ishiguro et al., 2013; Hara et al., 2014) came from the same RCT and were therefore recorded as Hara et al., 2014

	Experime		Contro		147	Risk Ratio	Risk Ratio	Risk of Bias
udy or Subgroup	Events	Total	Events	Total	weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
ang et al. 2015	16	33	15	33	19.8%	1.07 [0.64, 1.78]		
et al. 2015	20	30	15	30	19.8%	1.82 [1.07, 3.10]		
i et al. 2015	20	30	10	30	13.2%	2.10 [1.20, 3.67]		
et al. 2019	23	40	13	40	17.2%	1.77 [1.05, 2.98]		220000
ao et al. 2016a	15	30	6	30	7.9%	2.50 [1.12, 5.56]		
ra et al. 2014	63	164	12	68	22.4%	2.18 [1.26, 3.77]	_ <b>_</b> _	??
ao et al. 2017b	4	29	4	33	4.9%	1.14 [0.31, 4.15]		? • • • ? • •
btotal (95% CI)		356	-		100.0%	1.80 [1.43, 2.26]	•	
tal events	162		71					
terogeneity: Chi <sup>2</sup> =		(P = 0.4)		%				
st for overall effect:		•	1.					
.2 IGU only								
ao et al. 2016b	10	30	6	30	3.5%	1.67 [0.69, 4.00]		
et al. 2009a	53	163	70	163	40.3%	0.76 [0.57, 1.01]		
et al. 2009b	62	163	70	163	40.3%	0.89 [0.68, 1.15]	-	
et al. 2008a	9	92	6	95	3.4%	1.55 [0.57, 4.18]		
et al. 2008b	16	93	6	95	3.4%	2.72 [1.11, 6.66]		
ao et al. 2017a	4	34	4	33	2.3%	0.97 [0.26, 3.56]		
o et al. 2014a	5	30	6	30	3.5%	0.83 [0.28, 2.44]		
o et al. 2014b	4	30	6	30	3.5%	0.67 [0.21, 2.13]		
btotal (95% CI)		635		639	100.0%	0.94 [0.79, 1.12]	T	
tal events	163		174					
terogeneity: Chi <sup>2</sup> = st for overall effect:		•	//	36%				
		,						<b>—</b>
								20
st for subgroup diffe	rences Chi	i <sup>2</sup> - 10 /	15 df = 1		0001) 12 -	0/ 0%	Favours [control] Favours [exper	imental]
k of bias legend	Tences. On	1 - 13.4	io, ui – i (	F = 0.	0001), 1 =	54.576		
Random sequence	apporation	(select	ion hias)					
Allocation conceal	0	•	/					
Blinding of particip	(		,	ance hi	as)			
Blinding of outcom					(45)			
Incomplete outcom				,,				
Selective reporting			0)					
Other biases	(. sporting c							
RE 5								

(Ishiguro et al., 2013; Hara et al., 2014). Two records (Lu, 2014; Xia et al., 2016) came from the same RCT and were therefore recorded as Lu (2014); Xia et al. (2016). Therefore, 86 records actually involve 84 RCTs. In some RCTs, there were 2 experimental groups, and to match them, the control group was split into 2 equal parts with half the population each, and labeled as groups a and b (e.g., Xu et al., 2015a and Xu YM. et al., 2015). The included RCTs involved 4 rheumatic and autoimmune diseases (RA, AS, PSS and Autoimmune disease with interstitial pneumonia). The details of study characteristics are presented in Table 1.

# 3.3 Risk of bias assessments

The summary and graph of risk of bias ware shown in Figures 2, 3.

# 3.3.1 Sequence generation and allocation concealment

Fifty RCTs described detailed random sequence generation methods and were therefore assessed as low risk of bias, whereas the remainder were assessed as unclear risk of bias. Lü et al. (2008), Du et al. (2008), Tian et al. (2020), Zhao et al. (2017a), Li Y. et al.,

2021) and Shao et al. (2020) described methods of allocation concealment and was therefore assessed as low risk of bias, whereas the remainder were assessed as unclear risk of bias.

#### 3.3.2 Blinding

Zeng et al. (2016), Li Y. et al. (2021), and Donghui (2019) reported the use of blinding in their RCTs, but did not provide sufficient details about the implementation process, resulting in an unclear risk of bias assessment. Of the total 84 RCTs, 19 reported blinding of participants, and 18 reported blinding of assessors, indicating a low risk of bias. The remaining RCTs were assessed as high risk of bias because blinding was not described and outcomes included subjectively assessed outcomes.

# 3.3.3 Incomplete outcome data and selective reporting

Zhang (2018) and SShao et al. (2020) had incomplete outcomes and were therefore assessed as high risk of bias. There was not enough evidence to prove whether there were incomplete outcomes in Lu (2014), Xia et al. (2016), Li and WH (2020), Zhao et al. (2017a) and Jiang (2021), so they were assessed as unknown risk of bias. The remaining RCTs did not have incomplete outcomes and were therefore assessed as low risk of bias.



Mo et al. (2018) did not report all data planned in the methodology and was therefore assessed as high risk of bias. The remaining RCTs did not have selective reports and were therefore assessed as low risk of bias.

#### 3.3.4 Other potential bias

No other sources of bias were identified in any of the RCTs, indicating a low risk of bias from other sources.

# 3.4 IGU for RA

#### 3.4.1 RA remission rate

ACR20, ACR50 and ACR70 were used to represent RA remission rate. According to the medication of the IGU group, it is divided into IGU + MTX subgroup and IGU only subgroup.

For ACR20, the heterogeneity test showed that some subgroups had high heterogeneity (IGU + MTX subgroup: p = 0.005, I2 = 68%; IGU only subgroup: p = 0.20, I2 = 27%), and a random effect model was used. The meta-analysis findings indicate that the IGU + MTX group had a significantly lower ACR20 compared to the control group (RR 1.45 [1.14, 1.84], p = 0.003; random-effect model). However, there was no significant difference in ACR20 between the IGU-only group and the control

group (RR 0.99 [0.87, 1.13], p = 0.94; random-effect model) (Figure 4). The results of publication bias test showed that it was less likely to have publication bias in IGU + MTX subgroup (p = 0.313) and IGU only subgroup (p = 0.396).

For ACR50, the heterogeneity test showed that the heterogeneity was low (IGU + MTX subgroup: p = 0.44, I2 = 0%; IGU only subgroup: p = 0.14, I2 = 36%), and a fixed effect model was used. The meta-analysis findings indicate that the IGU + MTX group had a lower ACR50 compared to the control group (RR 1.80 [1.43, 2.26], p < 0.00001; fixed-effect model). However, there was no significant difference between the IGU only group and the control group (RR 0.94 [0.79, 1.12], p = 0.48; fixed-effect model) (Figure 5). The results of publication bias test showed that it was less likely to have publication bias in IGU + MTX subgroup (p = 0.433) and IGU only subgroup (p = 0.245).

For ACR70, the heterogeneity test showed that some subgroups had high heterogeneity (IGU + MTX subgroup: p = 0.74, I2 = 0%; IGU only subgroup: p = 0.02, I2 = 58%), and a random effect model was used. The findings of the meta-analysis indicate that the IGU + MTX group had a lower ACR70 than the control group (RR 1.84 [1.27, 2.67], p = 0.001; random effect model), while the difference between the IGU only group and the control group did not reach statistical significance (RR 1.51 [0.79, 2.86], p = 0.21; random effect model) (Figure 6). The results of publication

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% Cl	ABCDEFG
.4.1 IGU+MTX										
Deng et al. 2017a	2.3	0.05	31	2.7	0.02	16	5.3%	-0.40 [-0.42, -0.38]	•	??
(ie et al. 2018	2.62	1.21	39	4.81	1.67	39	4.9%	-2.19 [-2.84, -1.54]		??
(u et al. 2017	2.21	0.52	42	3.1	0.92	41	5.2%	-0.89 [-1.21, -0.57]	-	
3i et al. 2019	3.07	0.93	30	3.62	0.62	30	5.1%	-0.55 [-0.95, -0.15]	-	??
ïan et al. 2017	3.45	0.86	58	5.85	1.69	58	5.1%	-2.40 [-2.89, -1.91]	-	
Ciong et al. 2015	2.5	1.3	30	3.7	1.4	28	4.9%	-1.20 [-1.90, -0.50]		??
an et al. 2020	2.22	0.27	38	5.58	0.34	37	5.2%	-3.36 [-3.50, -3.22]	-	
hao et al. 2018	2.3	0.6	36	3.2	0.9	36	5.2%	-0.90 [-1.25, -0.55]	-	
i et al. 2020	5.1	0.7	20	3.16	1.01	13	4.9%	1.94 [1.31, 2.57]		
i et al. 2016	3.2	3.7	44	4.6	3.2	40	3.9%	-1.40 [-2.88, 0.08]		??
leng et al. 2015		1.27	33	3.23		33	5.0%	-0.31 [-0.88, 0.26]	-+	
hi et al. 2015	2	0.6	30	2.9	1.2	30	5.1%	-0.90 [-1.38, -0.42]		
lo et al. 2018		1.78	30	2.35		30	4.7%	0.21 [-0.66, 1.08]	- <u>-</u> -	
leng et al. 2016	3.02	1.24	30	5.65	1.86	30	4.8%	-2.63 [-3.43, -1.83]		??
/ang et al. 2019	2.62	0.36	47	3.77	0.5	46	5.2%	-1.15 [-1.33, -0.97]		??●●•••
u et al. 2020	3.15	1.21	58	5.87	1.73	58	5.0%	-2.72 [-3.26, -2.18]		
uan et al. 2015	2	0.6	30	2.9	1.2	30	5.1%	-0.90 [-1.38, -0.42]		??●●•••
lara et al. 2014	3.36	1.39	164	4.01	1.38	68	5.1%	-0.65 [-1.04, -0.26]		<b>??+++++</b>
ia et al. 2016a	1.7	0.6	44	2.59	0.56	25	5.2%	-0.89 [-1.17, -0.61]	-	??●●?++
hao et al. 2017b	-4.63	0.89	29	-3.76	0.6	16	5.1%	-0.87 [-1.31, -0.43]	<u></u>	? + + ? + +
ubtotal (95% CI)			863			704	100.0%	-1.11 [-1.69, -0.52]	◆	
. <b>4.2 IGU only</b> leng et al. 2017b	3.01	0.06	28	27	0.02	15	17.7%	0.31 [0.29, 0.33]		??
Cia et al. 2016b		0.56	38	2.59		24	17.1%	-0.16 [-0.45, 0.13]	-	220020
hao et al. 2017a	-3.43		34	-3.76	0.6	17	16.7%	0.33 [-0.05, 0.71]	<b> -</b> -	? • • • ? • •
lu et al. 2014		1.32	20	3.604		20	13.7%	-0.16 [-0.98, 0.65]		??
Dai et al. 2022	2.2	0.5	60	2.9	0.6	60	17.4%	-0.70 [-0.90, -0.50]	+	
Vu et al. 2022		0.51	58	3.58		58	17.3%	-1.40 [-1.65, -1.15]	+	
	2.10	0.01	238	0.00	0.04		100.0%	-0.30 [-0.94, 0.33]	<b>•</b>	
Subtotal (95% CI)					- 0.00					
ubtotal (95% CI) leterogeneity: Tau <sup>2</sup> = est for overall effect				f = 5 (P	< 0.00	1001); I	<sup>e</sup> = 98%			
leterogeneity: Tau <sup>2</sup> =	: Z = 0.94	(P = 0	.35)					Favo	I I I I -4 -2 0 2 4 Irs [experimental] Favours [control	1
teterogeneity: Tau <sup>2</sup> = est for overall effect est for subgroup diff <u>tisk of bias legend</u> A) Random sequenc B) Allocation concea C) Blinding of particip	: Z = 0.94 ferences: te general ilment (se pants and	Chi <sup>2</sup> = 0 Chi <sup>2</sup> = 1 tion (se	3.35) 3.35, d election bias) nnel (p	f = 1 (P bias) erforma	= 0.07	7), I² = 7		Favo		1
leterogeneity: Tau <sup>2</sup> = est for overall effect est for subgroup diff <u>kisk of bias legend</u> A) Random sequenc B) Allocation concea	: Z = 0.94 ferences: e general ilment (se pants and ne assess me data (a	Chi <sup>2</sup> = tion (se election f person sment ( attrition	3.35, d election bias) nnel (pr (detection bias)	f = 1 (P bias) erforma	= 0.07	7), I² = 7		Favol		 I
leterogeneity: Tau <sup>2</sup> = est for overall effect est for subgroup diff tisk of bias legend A) Random sequenc B) Allocation concea C) Blinding of outcom D) Blinding of outcom F) Selective reporting	: Z = 0.94 ferences: e general ilment (se pants and ne assess me data (a	Chi <sup>2</sup> = tion (se election f person sment ( attrition	3.35, d election bias) nnel (pr (detection bias)	f = 1 (P bias) erforma	= 0.07	7), I² = 7		Favou		1

bias test showed that it was less likely to have publication bias in IGU + MTX subgroup (p = 0.193) and IGU only subgroup (p = 0.230).

#### 3.4.2 DAS28

According to the medication of the IGU group, it is divided into IGU + MTX subgroup and IGU only subgroup. The heterogeneity test showed that the heterogeneity was high (IGU + MTX subgroup: p < 0.00001, I2 = 99%; IGU only subgroup: p < 0.00001, I2 = 98%), and a random effect model was used. According to the meta-analysis results, the IGU + MTX group showed a significant decrease in DAS28 compared to the control group (WMD -1.11 [-1.69, -0.52], p = 0.0002; random effect model). However, the difference between the IGU only group and control group was not statistically significant (WMD -0.30 [-0.94, 0.33], p = 0.35; random effect model) (Figure 7). The results of publication bias test showed that it may be likely to have publication bias in IGU + MTX subgroup (p = 0.080); but was less likely in and IGU only subgroup (p = 0.122).

#### 3.4.3 Inflammatory factor

Inflammatory factors include CRP, ESR and RF. According to the medication of the IGU group, it is divided into IGU + MTX subgroup, IGU only subgroup and IGU + Tripterygium Extract subgroup.

For CRP, the heterogeneity test showed that the heterogeneity was high (IGU + MTX subgroup: p < 0.00001, I2 = 95%; IGU only subgroup: p < 0.00001, I2 = 96%; IGU + Tripterygium Extract subgroup: p < 0.00001, I2 = 96%), and a random effect model was used. The meta-analysis results show that compared with the control group, the CRP in the IGU + MTX group, IGU only subgroup and IGU + Tripterygium Extract subgroup was lower (Figure 8).

For ESR, the heterogeneity test showed that the heterogeneity was high (IGU + MTX subgroup: p < 0.00001, I2 = 93%; IGU only subgroup: p < 0.00001, I2 = 96%; IGU + Tripterygium Extract subgroup: p < 0.00001, I2 = 96%), and a random effect model was used. The meta-analysis results show that compared with the control group, the ESR in the IGU + MTX group (WMD -11.05 [-14.58, -7.51], p < 0.00001;

tudy or Subgroup		erimen SD	tal Total		ontrol SD	Total \	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E F G
.5.1 IGU+MTX										
(u et al. 2015a	5.32	3.08	40	6.15	3.76	19	4.8%	-0.25 [-0.80, 0.30]	+	?? 🕈 🖨 🖶 🛨 🛨
Deng et al. 2017a	7	4	31	11	4	16	4.7%	-0.98 [-1.62, -0.35]	-	?? • • • • •
ian et al. 2020		35.35	76	9	34.9	59	4.9%	0.08 [-0.26, 0.43]	+	
									-	
u et al. 2017	22.18	7.71		34.43	9.29	41	4.8%	-1.42 [-1.91, -0.94]	-	
ian et al. 2017	12.69	4.18	58	19.38	5.12	58	4.9%	-1.42 [-1.83, -1.01]	-	
hen et al. 2018	17.24	3.63	60	25.11	3.42	60	4.9%	-2.22 [-2.68, -1.76]		
iong et al. 2015	8	3	30	19	5	28	4.6%	-2.65 [-3.37, -1.94]	-	<b>? ? • • • • •</b>
lo et al. 2015	30.65	30.81	30	48.25	31.83	30	4.8%	-0.55 [-1.07, -0.04]	٦	
hao et al. 2018	22.3	7.6	36	34.5	9.7	36	4.8%	-1.39 [-1.90, -0.87]	-	• ? • • • •
eng et al. 2017	3.46	0.07	60	7.4	1.02	60	4.5%	-5.42 [-6.20, -4.63]	-	?? 🗣 🗣 🗣 🛨
et al. 2016	5	5	44	10	6	40	4.9%	-0.90 [-1.35, -0.45]	-	?? 🕈 🖨 🛨 🛨
a et al. 2020	1.47	0.85	50	2.02	0.72	50	4.9%	-0.69 [-1.10, -0.29]	-	•?•••
hi et al. 2015	5.7	5.6	30	10.7	9	30	4.8%	-0.66 [-1.18, -0.14]	-	
								and a second framework and be a concerned.	-	
o et al. 2018	9.45	4.32	30	11.78	5.56	30	4.8%	-0.46 [-0.98, 0.05]	-	220000
ang et al. 2019	14.92	2.08	47	28.43	4.04	46	4.6%	-4.18 [-4.92, -3.45]		
i et al. 2019	11.6	12.1	40	18.4	13	40	4.9%	-0.54 [-0.98, -0.09]	_ 1	??
u et al. 2020	9.13	1.82		27.47	7.24	58	4.7%	-3.45 [-4.03, -2.87]	-	
uan et al. 2015	5.7	5.6	30	10.7	9	30	4.8%	-0.66 [-1.18, -0.14]	7	??
ara et al. 2014	1.31	2.18	164	1.83	1.85	68	5.0%	-0.25 [-0.53, 0.04]	1	<b>??</b> •••••
a et al. 2016a	5	2.52	44	14.99		25	4.8%	-1.55 [-2.11, -0.99]	-	?? 🕈 🛑 ? 🛨 🛨
nao et al. 2017b	5.69	0.8	29	19.9	7.39	16	4.3%	-3.16 [-4.08, -2.25]	- 1	<b>? • • • ? • •</b>
ubtotal (95% CI)	0.00	0.0	1029	.0.0			100.0%	-1.52 [-2.02, -1.02]	♦ [	
eterogeneity: Tau <sup>2</sup> =	1 28. 04	$i^2 = 422$		= 20 /0	< 0.00			tion [ nion, - tion]		
est for overall effect:				- 20 (P	× 0.00	501), I <sup>_</sup> =	90%			
5.2 IGU only										
	E 00	1.00		6 45	0.70	40	0.00/	0 10 10 70 0 141	Ļ	?? 🔴 🖨 🖶 🖨
u et al. 2015b	5.82	1.32	32	6.15	3.76	19	8.2%	-0.13 [-0.70, 0.44]	L	
eng et al. 2017b	16	6	28	11	4	15	8.0%	0.91 [0.25, 1.57]		??
a et al. 2016b	9.25	6.6	38	14.99	10.08	24	8.3%	-0.70 [-1.23, -0.17]	-	??●●?++
ara et al. 2007	-0.7	3.8	127	0.3	2.2	62	8.6%	-0.30 [-0.60, 0.01]	1	<b>? ? • • • • •</b>
u et al. 2009a	-8.8	31.9	163	-8.8	31.9	81	8.7%	0.00 [-0.27, 0.27]	t	
et al. 2009b	-6.6	26.3	163	-8.8	31.9	82	8.7%	0.08 [-0.19, 0.34]	+ +	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
i et al. 2008a	-2.09	12.12	92	0	15.26	47	8.6%	-0.16 [-0.51, 0.20]	+	
i et al. 2008b		19.55	93	0		48	8.6%	-0.10 [-0.45, 0.25]	+	
nao et al. 2017a	6.92	1.62	34	19.9	7.39	17	7.6%	-2.89 [-3.71, -2.06]	-	? • • • ? • •
nang et al. 2018	1.14	1.01	60	1.27	1.86	60	8.6%	-0.09 [-0.44, 0.27]	1	?? • • ? • •
-									-	
/ang et al. 2022	14.2	2.1	60	28.4	4	60	8.0%	-4.42 [-5.09, -3.75]	_	
ai et al. 2022	15.8	3.2	60	30.9	6.1	60	8.3%	-3.08 [-3.61, -2.55]	- <b>.</b>	
ubtotal (95% CI)			950				100.0%	-0.87 [-1.49, -0.25]	•	
eterogeneity: Tau <sup>2</sup> = est for overall effect:				= 11 (P	< 0.00	001); l² =	97%			
			,							
5.3 IGU+Tripterygiu u et al. 2022	um Extra 11.25	1.51	59	17.68	2.31	58	33.1%	-3.27 [-3.84, -2.71]	•	
	273.7	38.1		301.4	37.8		33.5%			
a et al. 2019a								-0.72 [-1.21, -0.24]	_1	
a et al. 2019b	273.7	38.1		312.5	33.9		33.4%	-1.09 [-1.59, -0.58]	<b>—</b>	
ubtotal (95% CI)	V 1007 1000	-	110				100.0%	-1.69 [-3.18, -0.19]	<b>▼</b>	
eterogeneity: Tau <sup>2</sup> = est for overall effect:				: 2 (P <	0.0000	1); I² = 96	6%			
stiol overall effect.	2 - 2.21	(1 - 0.	55)							
									-10 -5 0 5 10	
est for subgroup diffe	erences	Chi <sup>2</sup> = 2	2.87. df	= 2 (P :	= 0.24)	$ ^2 = 30.4$	%	Favou	rs [experimental] Favours [control]	
one group and				- (.	····/,					
ick of biog logond										
	~			oias)						
) Random sequence	ment (se									
A) Random sequence B) Allocation conceal		person	nel (pe	rforman	ice bias	)				
isk of bias legend A) Random sequence B) Allocation concealu C) Blinding of particip			detectio	n bias)						
<ul> <li>A) Random sequence</li> <li>Allocation conceale</li> <li>Blinding of particip</li> </ul>	ants and	sment (d		,						
<ul> <li>A) Random sequence</li> <li>B) Allocation concealing</li> <li>C) Blinding of particip</li> <li>D) Blinding of outcom</li> </ul>	ants and ne assess		bias)							
<ul> <li>A) Random sequence</li> <li>B) Allocation concealing</li> <li>C) Blinding of particip</li> <li>D) Blinding of outcom</li> <li>C) Incomplete outcom</li> </ul>	ants and ne assess ne data (a	attrition								
<ul> <li>a) Random sequence</li> <li>b) Allocation concealing</li> <li>c) Blinding of particip</li> <li>c) Blinding of outcom</li> <li>c) Incomplete outcom</li> <li>c) Selective reporting</li> </ul>	ants and ne assess ne data (a	attrition								
<ul> <li>a) Random sequences</li> <li>b) Allocation conceals</li> <li>c) Blinding of particip</li> <li>c) Blinding of outcom</li> <li>c) Incomplete outcom</li> <li>c) Selective reporting</li> <li>a) Other biases</li> </ul>	ants and ne assess ne data (a	attrition								
<ul> <li>A) Random sequence</li> <li>B) Allocation concealing</li> <li>C) Blinding of particip</li> <li>D) Blinding of outcom</li> </ul>	ants and ne assess ne data (a	attrition								

random effect model) and IGU + Tripterygium Extract group was lower (WMD –8.15 [–9.25, –7.05], p < 0.00001; random effect model), while its difference between IGU only group and control group was of no statistical significance (WMD –6.31 [–12.91, 0.29], p = 0.06; random effect model) (Figure 9).

For RF, the heterogeneity test showed that the heterogeneity was high (IGU + MTX subgroup: p < 0.00001, I2 = 97%; IGU only subgroup: p < 0.00001, I2 = 94%; IGU + Tripterygium Extract subgroup: p = 0.89,

I2 = 0%), and a random effect model was used. The meta-analysis results indicate that compared with the control group, the RF in the IGU + MTX group (SMD -1.65 [-2.48, -0.82], p < 0.0001; random effect model) and IGU + Tripterygium Extract group were significantly lower (SMD -1.34 [-1.61, -1.07], p < 0.00001; random effect model). However, there was no significant difference between the IGU only group and control group (SMD -0.37 [-1.00, 0.26], p = 0.25; random effect model) (Figure 10).



#### 3.4.4 Adverse events

According to the medication of the IGU group, it is divided into IGU + MTX subgroup, IGU only subgroup and IGU + Tripterygium Extract subgroup. The heterogeneity test showed that the heterogeneity was high (IGU + MTX subgroup: p = 0.64, I2 = 0%; IGU only subgroup: p = 0.003, I2 = 59%; IGU + Tripterygium Extract subgroup: p = 0.47, I2 = 0%), and a random effect model was used. The meta-analysis results show that compared with the control group, the adverse events in the IGU + MTX group was lower (RR 0.84 [0.78, 0.91], p < 0.00001; random effect model), while its difference between IGU only group and control group (RR 1.18 [0.89, 1.56], p = 0.26; random effect model), and between IGU + Tripterygium Extract and control group was of no statistical

significance (RR 1.10 [0.69, 1.77], p = 0.69; random effect model) (Figure 11). The results of publication bias test showed that it was less likely to have publication bias in IGU + MTX subgroup (p = 0.443) and in IGU only subgroup (p = 0.474).

#### 3.4.5 Quality of evidence

Only IGU + MTX and IGU only subgroups met the requirements of publication bias detection and evidence quality assessments.

According to the GRADE handbook, the evidence of IGU + MTX subgroup was judged to be moderate to very low (Table 2). The evidence of IGU only subgroup was judged to be moderate to low (Table 3).



# 3.5 IGU for AS

#### 3.5.1 BASDAI

Eight RCTs used BASDAI as an assessment tool to evaluate the effectiveness of IGU in improving AS. The included studies showed high heterogeneity, with p < 0.00001 and I2 = 86%, and thus a random effects model was used for analysis. The meta-analysis results showed that the IGU group had a significantly lower BASDAI score compared to the control group (SMD -1.62 [-2.20, -1.05], p < 0.00001; random effect model) (Figure 12). The results of publication bias test showed that it was less likely to have publication bias (p = 0.302).

#### 3.5.2 BASFI

Four RCTs were included in the meta-analysis, all of whom were assessed using BASFI to evaluate the improvement of AS. The heterogeneity test showed low heterogeneity, with p = 0.54 and I2 = 0%, indicating that a fixed effects model was appropriate for analysis. The results of the meta-analysis indicated that the IGU group had a significantly lower BASFI score compared to the control group (WMD -1.07 [-1.39, -0.75], p < 0.00001; fixed effect model) (Figure 13). The

results of publication bias test showed that it was less likely to have publication bias (p = 0.254).

### 3.5.3 VAS

Four RCTs were used to evaluate the effect of IGU on the improvement of AS through VAS, with a total of 137 patients in the IGU group and 135 patients in the control group. The heterogeneity test showed significant heterogeneity with p < 0.00001 and I2 = 95%, indicating the use of a random effects model for analysis. The meta-analysis results indicated a significant reduction in the VAS score for the IGU group compared to the control group (WMD –2.01 [–2.83, –1.19], p < 0.00001; random effects model) (Figure 14). The results of publication bias test showed that it may be likely to have publication bias (p = 0.071).

#### 3.5.4 Inflammatory factor

3.5.4.1 Inflammatory factors include ESR, CRP and TNF- $\!\alpha$ 

Six RCTs were included in the meta-analysis to evaluate the improvement of AS using ESR. High heterogeneity was observed (p < 0.00001, I2 = 90%), and therefore, a random effects model was used for the analysis. The results of the meta-analysis showed that the IGU group had a significantly lower ESR compared to the

Study or Subgroup	Experime Events		Contr vents		Weight M	Risk Ratio -H. Random, 95% Cl	Risk Ratio <u>M-H. Random. 95% Cl</u>	Risk of Bias A B C D E F G
1.8.1 IGU+MTX					-			
Zhao et al. 2017b	1	29	4	33	0.4%	0.28 [0.03, 2.40]		? • • • ? • •
Deng et al. 2017a	1	31	4	31	0.4%	0.25 [0.03, 2.11]		
Tian et al. 2020	72	120	94 7	119	8.1%	0.76 [0.64, 0.90]		??
Bi et al. 2019 Mong et al. 2015	4 2	30 33	1	30 33	1.4% 0.4%	0.57 [0.19, 1.75]		
Meng et al. 2015 Xiong et al. 2020	10	51	7	51	2.1%	2.00 [0.19, 21.00] 1.43 [0.59, 3.46]		
Xu et al. 2015a	8	40	7	38	2.1%	1.09 [0.44, 2.70]		2200000
Xie et al. 2018	4	39	7	39	1.4%	0.57 [0.18, 1.80]		2200000
Yan et al. 2018	9	35	8	35	2.3%	1.13 [0.49, 2.58]		??
Tian et al. 2017	4	58	5	58	1.2%	0.80 [0.23, 2.83]		
Chen et al. 2018	14	60	8	60	2.5%	1.75 [0.79, 3.86]		
Xiong et al. 2015	5	30	5	28	1.4%	0.93 [0.30, 2.88]		?? • • • • •
Mo et al. 2015	8	30	7	30	2.1%	1.14 [0.47, 2.75]		
Zhao et al. 2018	5	36	3	36	1.0%	1.67 [0.43, 6.46]		
Li et al. 2019	4	51	5	51	1.2%	0.80 [0.23, 2.81]		$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$ $\bullet$
Meng et al. 2017	13	60	11	60	2.8%	1.18 [0.58, 2.43]	- <b>-</b>	??
Shi et al. 2015	7	30	6	30	1.8%	1.17 [0.44, 3.06]		
Meng et al. 2016	2	30	1	30	0.4%	2.00 [0.19, 20.90]		??
Wang et al. 2019	6	47	4	46	1.3%	1.47 [0.44, 4.86]		??
Qi et al. 2019	23	40	20	40	5.3%	1.15 [0.76, 1.73]	+	??
Zhao et al. 2016a	5	30	9	30	1.8%	0.56 [0.21, 1.46]		• ? • • • • •
Duan et al. 2015	7	30	6	30	1.8%	1.17 [0.44, 3.06]		?? • • • • •
lara et al. 2014	132	164	66	68	8.9%	0.83 [0.76, 0.90]	-	??
i et al. 2016	5	44	6	40	1.5%	0.76 [0.25, 2.29]		?? • • • • •
No et al. 2018	2	30	3	30	0.7%	0.67 [0.12, 3.71]		
Subtotal (95% CI)		1178		1076	54.2%	0.84 [0.78, 0.91]	+	
otal events	353		304			e (19)		
leterogeneity: Tau <sup>2</sup> = 0 est for overall effect: 2	0.00; Chi <sup>2</sup> :			P = 0.64	4); I² = 0%			
1.8.2 IGU only								
Deng et al. 2017b	1	28	4	31	0.4%	0.28 [0.03, 2.33]		??
hao et al. 2016b	4	28	4	31	0.4% 1.6%	0.28 [0.03, 2.33] 0.44 [0.15, 1.29]		
u et al. 2015b	4 5	30	9	30	1.6%	0.44 [0.15, 1.29] 0.71 [0.25, 2.05]		2200000
ara et al. 20150	65	130	21	67	5.5%	1.60 [1.08, 2.37]	_ <b>_</b> _	224444
u et al. 2009a	65	163	75	163	7.2%	0.87 [0.67, 1.11]	-	
u et al. 2009a	79	163	75	163	7.5%	1.05 [0.84, 1.33]	+	
ü et al. 2008a	40	92	15	95	4.2%	2.75 [1.64, 4.63]		
ü et al. 2008b	32	93	15	95	4.2%	2.18 [1.27, 3.75]		
hao et al. 2017a	2	34	4	33	0.7%	0.49 [0.10, 2.47]		? • • • ? • •
lu et al. 2014	7	20	7	20	2.2%	1.00 [0.43, 2.33]		2200000
Shang et al. 2014	3	20	4	20	1.0%	0.75 [0.19, 2.93]		??
Zhang et al. 2018	3	57	2	58	0.6%	1.53 [0.26, 8.80]		??
Vang et al. 2022	6	60	5	60	1.4%	1.20 [0.39, 3.72]		
Sun and Li 2022	4	43	3	43	0.9%	1.33 [0.32, 5.61]	— <u> </u> ,	
Subtotal (95% CI)	-	971	5	916	38.9%	1.18 [0.89, 1.56]	•	
otal events	316		246					
leterogeneity: Tau <sup>2</sup> = 0 est for overall effect: Z	).12; Chi <sup>2</sup> :			P = 0.00	03); I² = 59%			
.8.3 IGU+Tripterygiu	n Extract							
Vu et al. 2022	6	58	7	58	1.6%	0.86 [0.31, 2.40]	<del></del>	• ? • • • • •
la et al. 2022	12	52	7	52	2.2%	1.71 [0.73, 4.01]	+	
1a et al. 2019b	12	52	13	52	3.0%	0 00 10 17 1 001	<u> </u>	
ubtotal (95% CI)	12	162	15	162	5.0% 6.9%	0.92 [0.47, 1.83] 1.10 [0.69, 1.77]	<b>•</b>	
otal events	30	102	27	102	0.070	1.10 [0.00, 1.77]	T	
otal events eterogeneity: Tau <sup>2</sup> = 0		= 1.52 df		0 47).	$l^2 = 0^{0/2}$			
est for overall effect: Z			- 2 (F =	0.47);	0 %			
otal (95% CI)		2311		2154	100.0%	1.05 [0.91, 1.21]	•	
otal events	699		577					
leterogeneity: Tau <sup>2</sup> = 0	0.06; Chi <sup>2</sup> :	= 80.97, d	f = 41 (I	P = 0.00	002); l <sup>2</sup> = 49%			-
est for overall effect: Z			,			0	.05 0.2 1 5 20 s [experimental] Favours [control]	
	ences: Ch	ni² = 6.10,	df = 2 (F	P = 0.05	5), I² = 67.2%	ravours	e [experimental] - ravou's [control]	
Test for subgroup differ	generatior	n (selection	n bias)					
Test for subgroup differ Risk of bias legend			,					
Fest for subgroup differ Risk of bias legend A) Random sequence	ient (selec		perform	ance bi	as)			
Test for subgroup differ Risk of bias legend A) Random sequence B) Allocation concealm		ersonnel (p						
Test for subgroup differ Risk of bias legend (A) Random sequence (B) Allocation concealm (C) Blinding of participa (D) Blinding of outcome	nts and pe		tion bias	s)				
Test for subgroup differ Risk of bias legend (A) Random sequence (B) Allocation concealm (C) Blinding of participa	nts and per assessme	ent (detec	tion bia	5)				
Test for subgroup differ Risk of bias legend A) Random sequence B) Allocation concealm C) Blinding of participa D) Blinding of outcome	nts and per assessme data (attr	ent (detec rition bias)	tion bia	5)				
est for subgroup differ <u>Risk of bias legend</u> A) Random sequence = B) Allocation concealm C) Blinding of participa D) Blinding of outcome E) Incomplete outcome	nts and per assessme data (attr	ent (detec rition bias)	tion bia	5)				
Test for subgroup differ Risk of bias legend A) Random sequence B) Allocation concealm C) Blinding of participa D) Blinding of outcome E) Incomplete outcome F) Selective reporting (	nts and per assessme data (attr	ent (detec rition bias)	lion bia:	5)				

control group (WMD –10.01 [–14.72, –5.29], p < 0.0001; random effect model) (Figure 15).

Six RCTs were included in the analysis of CRP to evaluate the improvement of AS. The heterogeneity test indicated

high heterogeneity (p < 0.00001, I2 = 98%), thus a random effects model was utilized for the analysis. The results of the meta-analysis demonstrated that IGU significantly decreased CRP levels compared to the control group

Outcomes	Illustrative c	comparative risks* (95% CI)	Relative effect	No of participants	Quality of the evidence	Comments
	Assumed risk	Corresponding risk	(95% CI)	(studies)	(GRADE)	
	Control					
ACR20 - IGU + MTX	Study populatio	n	RR 1.45	620 (7. studies)	⊕⊕⊝⊝ low <sup>a,b</sup>	
+ M1X	481 per 1,000	698 per 1,000 (548-885)	(1.14–1.84)	(7 studies)	IOW	
	Moderate					
	475 per 1,000	689 per 1,000 (541-874)				
ACR50 - IGU	Study populatio	n	RR 1.8	620	⊕⊕⊕⊝ la cab	
+ MTX	269 per 1,000	484 per 1,000 (385-608)	(1.43–2.26)	(7 studies)	moderate <sup>a,b</sup>	
	Moderate					
	325 per 1,000	585 per 1,000 (465-734)				
ACR70 - IGU	Study populatio	n	RR 1.84	620 (7. studies)	⊕⊕⊕⊙ moderate <sup>a,b</sup>	
+ MTX	129 per 1,000	237 per 1,000 (164-344)	(1.27–2.67)	(7 studies)	moderate	
	Moderate					
	150 per 1,000	276 per 1,000 (190-401)				
DAS28 - IGU + MTX		The mean DAS28-IGU + MTX in the intervention groups was 1.11 lower (1.69–0.52 lower)		1,567 (20 studies)	⊕000 very low <sup>a,b,c</sup>	
AEs - IGU	Study populatio	n	RR 0.84	2,254		
+ MTX	283 per 1,000	237 per 1,000 (220-257)	(0.78–0.91)	(25 studies)	moderate <sup>a</sup>	
	Moderate	·				
	179 per 1,000	150 per 1,000 (140-163)				

#### TABLE 2 Evidence quality of IGU for RA in IGU + MTX subgroup.

\*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: Risk ratio.

GRADE, working group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

<sup>a</sup>Downgraded one level due to serious risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcomes) and most of the data comes from the RCTs, with moderate risk of bias.

<sup>b</sup>Downgraded one level due to the probably substantial heterogeneity.

<sup>c</sup>Downgraded one level due to potential publication bias.

(WMD -7.90 [-12.01, -3.80], *p* < 0.00001; random effect model) (Figure 16).

# Three RCTs evaluated the effects of IGU on TNF- $\alpha$ levels in the treatment of AS. Significant heterogeneity was detected by the heterogeneity test (p < 0.00001, I2 = 95%), and a random effects model was applied for analysis. The results of the meta-analysis indicated that TNF- $\alpha$ levels were significantly lower in the IGU group compared to the control group (WMD -6.08 [-8.59, -3.58], p < 0.00001; random effects model) (Figure 17).

#### 3.5.5 Adverse events

A total of eight RCTs provided data on adverse events. The heterogeneity test indicated low heterogeneity with p = 0.48 and I2 = 0%, suggesting that a fixed effects model was appropriate for analysis. The meta-analysis indicated that there was no significant difference in adverse events between the IGU and control groups (RR 0.72 [0.47, 1.12], p = 0.15; fixed effect model) (Figure 18). The results of publication bias test showed that it was less likely to have publication bias (p = 0.766).

Outcomes	Illustrative c	omparative risks* (95% Cl)	Relative	No of	Quality of the	Comment
	Assumed risk	Corresponding risk	effect (95% CI)	participants (studies)	evidence (GRADE)	
	Control					
ACR20 - IGU	Study population	n	RR 0.99	1,429	⊕⊕⊕⊝	
only	471 per 1,000	467 per 1,000 (410-533)	(0.87-1.13)	(10 studies)	moderate <sup>a</sup>	
	Moderate					
	500 per 1,000	495 per 1,000 (435–565)				
ACR50 - IGU	Study population	n	RR 0.94	1,274	<b>⊕⊕⊕</b> ⊝	
only	272 per 1,000	256 per 1,000 (215-305)	(0.79–1.12)	(8 studies)	moderate <sup>a</sup>	
	Moderate					
	200 per 1,000	188 per 1,000 (158-224)				
ACR70 - IGU	Study population	n	RR 1.51	1,274	000 00	
only	121 per 1,000	182 per 1,000 (95-345)	(0.79–2.86)	(8 studies)	low <sup>a,b</sup>	
	Moderate					
	50 per 1,000	76 per 1,000 (40-143)				
DAS28 - IGU only		The mean DAS28-IGU only in the intervention groups was 0.3 lower (0.94 lower to 0.33 higher)		432 (6 studies)	⊕⊕⊝⊝ low <sup>a,b</sup>	
AEs - IGU only	Study population	n	RR 1.18	1887	<b>⊕⊕⊙⊙</b>	
	269 per 1,000	317 per 1,000 (239–419)	(0.89–1.56)	(14 studies)	low <sup>a,b</sup>	
	Moderate					
	171 per 1,000	202 per 1,000 (152-267)				

#### TABLE 3 Evidence quality of IGU for RA in IGU only subgroup.

<sup>a</sup>Downgraded one level due to serious risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcomes) and most of the data comes from the RCTs, with moderate risk of bias.

<sup>b</sup>Downgraded one level due to the probably substantial heterogeneity.

#### 3.5.6 Quality of evidence

According to the GRADE handbook, the evidence was judged to be moderate to very low (Table 4).

# 3.6 IGU for PSS

#### 3.6.1 ESSPRI

The heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p < 0.0001, I2 = 96%; IGU only subgroup: p < 0.0001, I2 = 78%), and a random effect model was used. The meta-analysis results show that compared with the control group, the ESSPRI in the IGU + other therapy group (WMD -1.71 [-2.44, -0.98], p < 0.00001; random effect model) and IGU only group (WMD -2.10 [-2.40, -1.81], p < 0.00001; random effect model) was lower (Figure 19). The results of

publication bias test showed that it was less likely to have publication bias in IGU + other therapy subgroup (p = 0.667), while the publication bias test showed that it was likely to have publication bias in IGU only subgroup (p = 0.066).

# 3.6.2 ESSDAI

The heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p < 0.00001, I2 = 90%; IGU only subgroup: p = 0.80, I2 = 0%), and a random effect model was used. The meta-analysis results show that compared with the control group, the ESSDAI in the IGU + other therapy group (WMD -1.62 [-2.30, -0.94], p < 0.00001; random effect model) and IGU only group (WMD -1.51 [-1.65, -1.37], p < 0.00001; random effect model) was lower (Figure 20). The results of publication bias test showed that it was less likely to have publication bias in IGU + other therapy (p = 0.691) and IGU only subgroup (p = 0.659).

	Expe	erimen	tal	С	ontrol		5	Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	ABCDEFG
Qiu et al. 2016	2.7	1.5	18	4.6	1.5	18	11.9%	-1.24 [-1.96, -0.52]	-	
Pang et al. 2020	1.28	0.41	39	2.86	0.53	39	12.1%	-3.30 [-3.99, -2.61]	-	• ? • • • • •
Lin et al. 2019	1.92	0.81	24	3.07	1.15	24	12.6%	-1.14 [-1.75, -0.52]	-	
Xu et al. 2019	3.8	1.1	21	4.7	0.7	21	12.4%	-0.96 [-1.60, -0.32]	•	
Zeng et al 2016	1.86	0.89	25	2.49	0.9	25	12.8%	-0.69 [-1.26, -0.12]	-	• ? ? ? • • •
Yan et al. 2021	1.33	0.81	48	3.04	0.96	25	12.7%	-1.96 [-2.54, -1.38]	-	•••??•••
Bai et al. 2021		0.83	42	3.05		43	13.4%	-1.30 [-1.77, -0.83]		
Li et al. 2021	10.06	2.75	30	16.85	2.59	30	12.1%	-2.51 [-3.20, -1.82]	-	
Total (95% CI)			247			225	100.0%	-1.62 [-2.20, -1.05]	•	
Heterogeneity: Tau <sup>2</sup> =	: 0.59; Ch	ni² = 49	.41, df	= 7 (P <	< 0.000	01); l <sup>2</sup>	= 86%	_	-10 -5 0 5 10	-
Test for overall effect	Z = 5.53	(P < 0	.00001	)				Four	-10 -5 0 5 10 burs [experimental] Favours [control]	
								Favo	suis [experimental] Favours [control]	
Risk of bias legend										
(A) Random sequenc	e generat	tion (se	election	bias)						
(B) Allocation concea	ment (se	lection	bias)							
	ants and	perso	nnel (pe	erforma	nce bia	as)				
(C) Blinding of particip	assess	sment	detecti	on bias	)					
<ul> <li>(C) Blinding of particip</li> <li>(D) Blinding of outcom</li> </ul>	10 400000	a thaiting a	bias)							
		attritior								
(D) Blinding of outcon	ne data (a									
(D) Blinding of outcon (E) Incomplete outcor	ne data (a									
<ul> <li>(D) Blinding of outcom</li> <li>(E) Incomplete outcom</li> <li>(F) Selective reporting</li> </ul>	ne data (a									
<ul> <li>(D) Blinding of outcom</li> <li>(E) Incomplete outcom</li> <li>(F) Selective reporting</li> </ul>	ne data (a									

	Expe	riment	al	C	ontrol			Mean Difference	Mean Difference	Risk of Bias				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl	ABCDEFG				
Qiu et al. 2016	2.9	1.8	18	4.6	1.5	18	8.7%	-1.70 [-2.78, -0.62]		• ? • • • •				
Lin et al. 2019	2.06	0.92	24	3.28	1.14	24	29.7%	-1.22 [-1.81, -0.63]	-	• ? • • • •				
Xu et al. 2019	3.4	1.2	21	4.3	1.1	21	21.1%	-0.90 [-1.60, -0.20]		• ? • • • •				
Yan et al. 2021	1.15	0.78	48	2.06	1.15	25	40.5%	-0.91 [-1.41, -0.41]	-	•••??				
Total (95% CI)			111			88	100.0%	-1.07 [-1.39, -0.75]	•					
Heterogeneity: Chi <sup>2</sup> = 2	2.17, df =	= 3 (P =	0.54);	$I^2 = 0\%$	5					-				
Test for overall effect:	Test for overall effect: $Z = 6.56$ (P < 0.0001) Favours [experimental] Favours [control]													
Risk of bias legend (A) Random sequence (B) Allocation conceal (C) Blinding of particip (D) Blinding of outcom (E) Incomplete outcom (F) Selective reporting (G) Other biases	ment (sel ants and e assess ne data (a	ection l person ment (o attrition	bias) inel (pe detectio bias)	erforma		as)								
FIGURE 13 The results of BASFI.														

		Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
-	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	ABCDEFG
	Qiu et al. 2016	3.7	2	18	6.3	1.6	18	15.6%	-2.60 [-3.78, -1.42]	_	• ? • • • • •
	Yuan et al. 2020	1.02	0.3	41	3.95	0.58	39	22.3%	-2.93 [-3.13, -2.73]	•	• ? • • • • •
	Lin et al. 2019	2.56	1.42	24	4.17	1.69	24	18.1%	-1.61 [-2.49, -0.73]		• ? • • • • •
	Xu et al. 2019	4.1	0.6	21	6	0.3	21	22.1%	-1.90 [-2.19, -1.61]	•	• ? • • • • •
	Bai et al. 2021	2.03	0.83	42	3.11	0.73	43	21.9%	-1.08 [-1.41, -0.75]	-	+?+++++++++++++++++++++++++++++++++++++
	Total (95% CI)			146			145	100.0%	-2.01 [-2.85, -1.17]	•	
	. ,	0.00.04	12 - 00		- 4 (D	. 0. 000			-2.01[-2.03, -1.17]		-
	Heterogeneity: Tau <sup>2</sup> =					0.000	JUT); I-	= 90%		-4 -2 0 2 4	
	Test for overall effect:	2 = 4.67	(P < 0	.00001	)				Favou	Irs [experimental] Favours [control]	
	Disk of bigs logged										
	Risk of bias legend		ion (oo	lastian	hine)						
	(A) Random sequence				blas)						
	(B) Allocation conceal										
	(C) Blinding of participa						as)				
	(D) Blinding of outcome				on blas	)					
	(E) Incomplete outcom	,									
	(F) Selective reporting	(reportin	g bias)	)							
	(G) Other biases										
FIG	URE 14										
The	e results of VAS.										



		Exp	eriment	al	C	ontrol			Mean Difference	Mean Difference	Risk of Bias				
-	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG				
	Yuan et al. 2020	9.37	1.02	41	22.03	1.56	39	19.1%	-12.66 [-13.24, -12.08]	•					
	Pang et al. 2020	10.22	2.14	39	17.45	3.85	39	18.8%	-7.23 [-8.61, -5.85]						
	Xu et al. 2019	14.3	8.8	21	23.5	15.1	21	11.7%	-9.20 [-16.67, -1.73]						
	Zeng et al 2016	6.21	1.53	25	15.31	3.66	25	18.7%	-9.10 [-10.66, -7.54]	•	•???•••				
	Yan et al. 2021	6.81	10.85	48	12.21	14.97	25	12.8%	-5.40 [-12.02, 1.22]	-	•••??•••				
	Bai et al. 2021	5.43	1.83	42	8.92	2.91	43	18.9%	-3.49 [-4.52, -2.46]	-	• ? • • • • •				
	Total (95% CI)			216			192	100.0%	-7.90 [-12.01, -3.80]	•					
	Heterogeneity: Tau <sup>2</sup> = :	22.91; C	hi² = 25	2.37, d	f = 5 (P	< 0.000	001); l <sup>2</sup>	= 98%							
	Heterogeneity: Tau <sup>2</sup> = 22.91; Chi <sup>2</sup> = 252.37, df = 5 (P < 0.00001); l <sup>2</sup> = 98% Test for overall effect: Z = 3.77 (P = 0.0002) Favours [control]														
	Test for overall effect: Z = 3.77 (P = 0.0002)       Favours [experimental]       Favours [control]														
	Risk of bias legend														
	(A) Random sequence	generat	ion (sele	ection b	oias)										
	(B) Allocation conceal	nent (se	lection b	oias)											
	(C) Blinding of participa	ants and	person	nel (pe	forman	ce bias	)								
	(D) Blinding of outcome														
	(E) Incomplete outcom														
	(F) Selective reporting			oldo)											
	(G) Other biases	(reportin	g blas												
FIC															
	URE 16														
The	results of CRP.														

## 3.6.3 Schirmer's test

The heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p = 0.02, I2 = 63%; IGU only subgroup: p < 0.00001, I2 = 99%), and a random effect model was used. The meta-analysis results show that compared with the control group, the schirmer's test in the IGU + other therapy group (WMD 2.18 [1.76, 2.59], p <0.00001; random effect model) and IGU only group (WMD 1.55 [0.35, 2.75], p = 0.01; random effect model) was higher (Figure 21). The results of publication bias test showed that it was less likely to have publication bias in IGU + other therapy (p = 0.612) and IGU only subgroup (p = 0.934).

#### 3.6.4 Inflammation factors

Inflammation factors include ESR, CRP and RF.

For ESR, the heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p < 0.00001, I2 = 95%; IGU only subgroup: p < 0.00001, I2 = 95%),

and a random effect model was used. The meta-analysis results show that compared with the control group, the ESR in the IGU + other therapy group (WMD -8.80 [-11.88, -5.72], p < 0.00001; random effect model) and IGU only group (WMD -4.97 [-7.41, -2.54], p < 0.0001; random effect model) was lower (Figure 22).

For CRP, the heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p < 0.00001, I2 = 93%; IGU only subgroup: not applicable), and a random effect model was used. The meta-analysis results show that compared with the control group, the CRP in the IGU + other therapy group was lower (SMD -1.16 [-2.31, -0.00], p = 0.05; random effect model) (Figure 23).

For RF, the heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p < 0.00001, I2 = 88%; IGU only subgroup: p < 0.00001, I2 = 83%), and a random effect model was used. The meta-analysis results show that compared with the control group, the RF in the IGU + other





therapy group (WMD -6.44 [-8.05, -4.83], p < 0.00001; random effect model) and IGU only group (WMD -4.42 [-5.94, -2.90], p < 0.0001; random effect model) was lower (Figure 24).

#### 3.6.5 Adverse events

The heterogeneity test showed that some subgroups had high heterogeneity (IGU + other therapy subgroup: p = 0.95, I2 = 0%; IGU only subgroup: p = 0.49, I2 = 0%), and a fixed effect model was used. The meta-analysis results show that compared with the control group, the incidence of adverse events in the IGU only group (RR 0.66 [0.48, 0.98], p = 0.01; fixed effect model) was lower, while the difference of the incidence of adverse events between IGU + other therapy group and control grouo was of no statistical significance (RR 0.94 [0.68, 1.29], p = 0.68; fixed effect model) was lower (Figure 25). The results of publication bias test showed that it was less likely to have publication bias in IGU + other therapy (p = 0.777) and IGU only subgroup (p = 0.501).

## 3.6.6 Quality of evidence

According to the GRADE handbook, the evidence of IGU + other therapy subgroup was judged to be moderate to low (Table 5). The evidence of IGU only subgroup was judged to be moderate to very low (Table 6).

# 3.7 IGU for autoimmune disease with interstitial pneumonia

Zhuang et al. (2021) and Zhang et al. (2019) reported the treatment of PSS with interstitial pneumonia. DongZhang et al. (2019) reported the treatment of RA with interstitial pneumonia. Zhang et al. (2019) and DongZhang et al. (2019) reported FVC; they found that IGU may improve FVC.

Meanwhile, Zhuang et al. (2021) showed that both DLCO and 6MWT improved in both groups after treatment, and the degree of

	1 7					
Outcomes	Illustrative co	omparative risks* (95% Cl)	Relative effect (95% Cl)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk		(studies)		
	Control	Adverse event				
BASDAI		The mean basdai in the intervention groups was 1.62 standard deviations lower (2.2–1.05 lower)		472 (8 studies)	⊕⊕⊖⊖ low <sup>a,b</sup>	SMD -1.62 (-2.2 to -1.05)
BASFI		The mean basfi in the intervention groups was 1.07 lower (1.39–0.75 lower)		199 (4 studies)	⊕⊕⊕⊙ moderate <sup>a</sup>	
VAS		The mean vas in the intervention groups was 2.01 lower (2.85–1.17 lower)		291 (5 studies)	⊕⊙⊝⊙ very low <sup>a,b,c</sup>	
Adverse events	Study population	1	RR 0.73 (0.47–1.12)	473 (8 studies)	⊕⊕⊕⊙ moderateª	
	179 per 1,000	130 per 1,000 (84–200)	(0.4/-1.12)	(8 studies)	moderate	
	Moderate					
	175 per 1,000	128 per 1,000 (82-196)	Ť			

#### TABLE 4 Evidence quality of IGU for AS.

<sup>a</sup>Downgraded one level due to serious risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcomes) and most of the data comes from the RCTs, with moderate risk of bias.

<sup>b</sup>Downgraded one level due to the probably substantial heterogeneity.

<sup>c</sup>Downgraded one level due to potential publication bias.

improvement in 6MWT in the IGU group was due to that in the control group. Zhang et al. (2019) reported that MMF was also improved after treatment, and the improvement was greater in the IGU group than in the control group. DongZhang et al. (2019) showed that compared with the control group, both FEV1 and TLC were improved after IGU treatment (p < 0.05).

# 4 Discussion

### 4.1 IGU for RA

IGU was approved for the treatment of RA in China and Japan in 2012, and in the RA guidelines of the Asia Pacific Association of Rheumatology (APLAR) meeting in 2014. It is recommended as an effective option for intensive treatment of refractory RA (Li et al., 2013; Li J. et al., 2019). It is now widely used to treat autoimmune diseases and improve related inflammation, such as PSS, IgG4related diseases, lupus nephritis, *etc.* (Nozaki, 2021). Studies have shown that compared with other traditional DMARDs drugs, IGU can not only inhibit the production of immunoglobulin and various inflammatory cytokines (IL-1, IL-6, IL-8 and TNF), promote the differentiation of bone cells, inhibit the generation of osteoclasts, reduce bone resorption and joint destruction, but also reduce the expression of matrix metalloproteinases by inhibiting the production of MMP-1 and MMP-3, thereby playing an antiinflammatory role (Liu et al., 2021a; Mizutani et al., 2021; Mu et al., 2021; Tanaka, 2021). In addition, IGU can also inhibit COX-2 and reduce the short-term synergistic effect of pain and inflammation (Mu et al., 2021; Tanaka, 2021).

This meta-analysis found that IGU + MTX therapy can improve ACR20, ACR50, ACR70, DAS28, reduce ESR, CRP, RF, and have a lower incidence of adverse events than the control group. However, IGU alone only significantly improved CRP. IGU + Tripterygium Extract can also improve ESR, CRP and RF. This suggests that IGU + MTX may be a better combination of IGU in the treatment of RA, because it has obvious efficacy, can reduce inflammatory factors, and has a lower incidence of adverse events than the control group therapy (mainly MTX). There is heterogeneity in most outcomes, which is considered to be related to the following points: 1) the dose and duration of IGU and MTX are different; 2) the degree of disease activity of patients at baseline is not the same. Since the extent of disease activity in patients at baseline was not clearly stated in each study, further analysis was not performed. In addition, the dose of IGU in all RCTs was 25-50 mg (25 mg Bid for most RCTs; and 25 Qd or 50 mg Qd for a few RCTs), suggesting that IGU at this dose had a good effect on RA without increasing the incidence of adverse events.

A recent 52-week randomized, double-blind, parallel-controlled, multicenter study by Bao et al. showed that IGU (Use alone) was more effective than MTX in the treatment of RA (Du F. et al., 2021). In terms of efficacy, the ACR20 response rate of IGU was 77.44%,

tudy or Subgroup		erimen			ontrol		Moight	Mean Difference IV, Random, 95% CI	Mean Difference IV. Random, 95% CI	Risk of Bias A B C D E F G
.1.1 IGU+other therapy		30	TOLA	mean	30	TOtal	weight	rv, Random, 95% Cl		ABCDEFG
hang and Shen 2019		0.76	43	4.45	1.01	43	14.8%	-1.76 [-2.14, -1.38]	-	
iang et al. 2021		0.39	43 30	4.45		43 30	14.8%	-1.08 [-1.31, -0.85]	•	
lang et al. 2021 lang et al. 2019	2.23	1.1	32	5.2		32		-2.40 [-2.99, -1.81]	-	
hen et al. 2022		0.82	62	5.33			14.9%	-2.93 [-3.26, -2.60]	- ·	
ang et al. 2021		0.89	24	1.69			14.5%	-0.01 [-0.47, 0.45]	+	<b>? ? • • ? • •</b>
ing et al. 2022		1.29	20		1.72		12.2%	-2.21 [-3.15, -1.27]		??
iu 2022		0.83	40		1.11	40	14.6%	-1.68 [-2.11, -1.25]	-	
ubtotal (95% CI)	2	0.00	251				100.0%	-1.71 [-2.44, -0.98]	◆	
eterogeneity: Tau <sup>2</sup> = 0.9	90: Chi <sup>2</sup>	= 136.	89. df =	= 6 (P <	0.000					
est for overall effect: Z :				0 (.	0.000	.,,.	0070			
			,							
.1.2 IGU only										
u et al. 2017	2.7	1.4	47	5.3	1.1	47	11.4%	-2.60 [-3.11, -2.09]	-	
a 2020	2.71	0.76	43	4.54	1.19	43	12.7%	-1.83 [-2.25, -1.41]	-	
ang et al. 2020	2.92	0.19	25	4.64	0.15	25	16.8%	-1.72 [-1.81, -1.63]	•	??
hao et al. 2020	3	1.2	26	4	2.8	19	3.8%	-1.00 [-2.34, 0.34]		
iu 2022	2.75	0.81	42	4.66	1.22	42	12.4%	-1.91 [-2.35, -1.47]	-	
ang et al. 2014	2.9	1.4	25	5.1	1.4	25	7.9%	-2.20 [-2.98, -1.42]		??
ai et al. 2019	2.8	1.3	30	5	1.3	30	9.3%	-2.20 [-2.86, -1.54]		•?••••
i et al. 2018	2.74	0.71	34	5.2	0.86	34	13.5%	-2.46 [-2.83, -2.09]	-	
i et al. 2020	2.73	0.72	23	5.21	0.87	23	12.1%	-2.48 [-2.94, -2.02]	<b>T</b>	??
ubtotal (95% CI)			295				100.0%	-2.10 [-2.40, -1.81]	•	
eterogeneity: Tau <sup>2</sup> = 0.					0.0001	); $ ^2 = 7$	8%			
est for overall effect: Z =	= 13.84	(P < 0.	00001)							
									-4 -2 0 2 4	
		L 12 0	00 16	4 (5	0.001	12 00/		Fav	ours [experimental] Favours [control]	
est for subgroup differe	nces: C	$n_{1^{*}} = 0.$	96, df =	= 1 (P =	0.33),	$1^2 = 0\%$	D			
isk of bias legend										
A) Random sequence g		•		as)						
B) Allocation concealme										
c) Blinding of participant					e bias	)				
0) Blinding of outcome a				i bias)						
E) Incomplete outcome			las)							
F) Selective reporting (re	eporting	blas)								
G) Other biases										
RE 19										

which was significantly better than that of MTX (65.87%). In the direction of imaging improvement, the results showed that the proportion of patients with no imaging progression in IGU or combined therapy for 1 year was higher than that in MTX therapy, indicating that IGU therapy was significantly better than MTX therapy. The efficacy of IGU + MTX is similar to that of IGU only, suggesting that patients with early RA can consider IGU alone, and only when the single drug is not effective, combined with other drugs such as biological agents. They also found that IGU or combination therapy can delay the imaging progress of RA patients, which provides an important reference for clinical medication. Another important factor for RA patients and doctors when choosing a drug is the efficacy, safety and cost of the drug. Jie et al. reported data from a real-world pharmacoeconomics study on IGU and other drugs in RA at the 2022 EULAR meeting. Their results show that IGU combined with MTX in the treatment of RA is both safe and effective, and the price is moderate, providing a treatment plan for RA patients that takes into account efficacy, safety and economic cost.

# 4.2 IGU for AS

The current study shows that IGU, as a new type of DMARD, mainly acts through anti-inflammatory and immune regulation. For example, IGU can inhibit the production of inflammatory cytokines (such as IL-1 and TNF- $\alpha$ ), block the IL-17 signaling pathway and inhibit cyclooxygenase, and regulate the balance of osteoclasts (Liu et al., 2021b; Harjacek, 2021), so it may be effective against AS/SpA in mechanism. Therefore, a number of exploratory RCTs have previously applied IGU to AS/SpA (Qiu et al., 2016; Zeng et al., 2016; Lin et al., 2019; Xu et al., 2019; Pang et al., 2020; Yuan et al., 2020; Li Y. et al., 2021; Bai et al., 2021; Li X. et al., 2021).

The meta-analysis findings revealed that IGU was effective in reducing the BASDAI score, BASFI score, and VAS. Additionally, IGU was able to lower inflammation levels by decreasing ESR, CRP, and TNF-a. However, there was considerable heterogeneity in the results, especially in VAS, ESR, CRP, and TNF-a. This could be attributed to the fact that BASDAI and VAS are subjective measures, and the experiences of patients across different RCTs may differ. Moreover, ESR, CRP, and TNF-a are individual biochemical indicators, and variations in patients' conditions across different RCTs may also contribute to the heterogeneity. All RCTs reported adverse events, but no patient deaths were recorded. Compared to the control group, the IGU group did not experience any statistically significant difference in adverse events. Therefore, IGU does not appear to increase the risk of adverse events. Notably, the IGU dose was 50 mg in all RCTs (25 mg Bid in most RCTs and 50 mg Qd in a few RCTs), indicating that this dose had a beneficial effect on AS without raising the incidence of adverse events.

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference	<b>Risk of Bias</b>
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	ABCDEFG
1.2.1 IGU+other thera	ру									
Zhang and Shen 2019	6.68	1.75	43	8.33	1.52	43	12.4%	-1.65 [-2.34, -0.96]	-	
Zhang 2019	6.38	1.32	60	8.85	1.2	60	13.4%	-2.47 [-2.92, -2.02]	-	?? 🕈 🖶 🖶 🗣
Liang et al. 2021	6.08	0.58	30	7.19	0.85	30	13.6%	-1.11 [-1.48, -0.74]	-	•?•••
Wang et al. 2019	6.5	1.7	32	8.1	1.2	32	12.3%	-1.60 [-2.32, -0.88]	-	
Chen et al. 2022	5.73	1.1	62	8.36	2.64	62	12.3%	-2.63 [-3.34, -1.92]	-	
Jiang et al. 2021	2.14	1.21	24	1.75	0.9	22	12.7%	0.39 [-0.22, 1.00]	-	?? 🗣 🗣 ? 🗣 🗣
Ding et al. 2022	6.56	1.26	20	8.88	1.78	20	11.1%	-2.32 [-3.28, -1.36]		?? 🗣 🖶 🛨 🛨
Liu 2022	6.59	1.72	40	8.29	1.63	40	12.2%	-1.70 [-2.43, -0.97]	-	• ? • • • • •
Subtotal (95% CI)			311			309	100.0%	-1.62 [-2.30, -0.94]	•	
Heterogeneity: Tau <sup>2</sup> = 0	).86; Chi <sup>2</sup>	= 71.4	19, df =	7 (P < 0	0.0000	1); l² =	90%			
Test for overall effect: 2	2 = 4.65 (	P < 0.0	00001)							
1.2.2 IGU only										
Xu et al. 2017	6.7	1.5	47	8.3	1.4	47	6.1%	-1.60 [-2.19, -1.01]	-	•?••+
Jia 2020	6.51	1.56	43	8.44	1.93	43	3.8%	-1.93 [-2.67, -1.19]	-	
Jiang et al. 2020	4.32	0.29	25	5.8	0.28	25	83.5%	-1.48 [-1.64, -1.32]		?? 🗣 🗣 🗣 🗣
Shao et al. 2020	8.6	5.4	26	8	9.5	19	0.1%	0.60 [-4.15, 5.35]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Jiang et al. 2014	6.4	1.8	25	8	1	25	3.2%	-1.60 [-2.41, -0.79]		??●●●●●
Bai et al. 2019	6.5	1.9	30	8.1	1.1	30	3.4%	-1.60 [-2.39, -0.81]	<u> </u>	$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$
Subtotal (95% CI)			196			189	100.0%	-1.51 [-1.65, -1.37]	•	
Heterogeneity: Tau <sup>2</sup> = 0					80); l²	= 0%				
Test for overall effect: 2	2 = 20.50	(P < 0	.00001	)						
									-4 -2 0 2 4	_
								Favour	rs [experimental] Favours [control]	
Test for subgroup differ	ences: C	$hi^2 = 0$	.10, df :	= 1 (P =	0.76),	$ ^2 = 0\%$	0		[	
Risk of bias legend										
(A) Random sequence				ias)						
(B) Allocation concealm										
(C) Blinding of participa					ce bias	)				
(D) Blinding of outcome		,		n bias)						
(E) Incomplete outcome			oias)							
(F) Selective reporting (	reporting	bias)								

#### FIGURE 20

Essdai.

	Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
1.3.1 IGU+other therap	ру									
Nang et al. 2019	5.5	1.3	32	2.7	0.8	32	19.4%	2.80 [2.27, 3.33]	•	
Kie et al. 2020	7.83	3.1	38	5.8	1.3	38	9.8%	2.03 [0.96, 3.10]	-	$\bullet ? \bullet \bullet \bullet \bullet \bullet$
Zhang and Shen 2019	5.57	1.71	43	3.98	1.15	43	17.4%	1.59 [0.97, 2.21]	-	$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$ $\bullet$
hang 2019	5.65	1.09	60	3.29	1.05	60	22.8%	2.36 [1.98, 2.74]		?? 🕈 🖶 🖶 🛨 🛨
Ding et al. 2022	5.53	1.32	20	2.99	1.38	20	13.2%	2.54 [1.70, 3.38]	-	?? 🕈 🖶 🖶 🛨 🛨
iu 2022	5.64	1.68	40	4.01	1.07	40	17.4%	1.63 [1.01, 2.25]		• ? • • • • •
Subtotal (95% CI)			233			233	100.0%	2.18 [1.76, 2.59]	•	
Heterogeneity: Tau <sup>2</sup> = 0	).16; Chi <sup>2</sup>	= 13.3	4, df = 5	5 (P = 0	0.02); I	<sup>2</sup> = 63%				
lest for overall effect: 2	2 = 10.28	(P < 0.	00001)							
.3.2 IGU only										
liang et al. 2020	4.67	0.31	25	2.25	0.11	25	21.9%	2.42 [2.29, 2.55]		<b>??</b>
Shao et al. 2020	5.4	3.2	26	4.6	3.5	19	13.7%	0.80 [-1.20, 2.80]		
liang et al. 2014	5.3	1.1	25	2	1	25	20.9%	3.30 [2.72, 3.88]		??
(u et al. 2017	1.4	0.45	47	1.1	0.14	47	21.9%	0.30 [0.17, 0.43]	•	
	3 92	0.58	43	3.21	0.51	43	21.8%	0.71 [0.48, 0.94]		$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$ $\bullet$
Rao et al. 2022	0.02									
Rao et al. 2022 Subtotal (95% CI)	0.02		166			159	100.0%	1.55 [0.35, 2.75]		
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1	I.71; Chi²	= 570.	67, df =	4 (P <	0.000			1.55 [0.35, 2.75]		
Subtotal (95% CI)	I.71; Chi²	= 570.	67, df =	4 (P <	0.000			1.55 [0.35, 2.75]	•	
Subtotal (95% CI) leterogeneity: Tau <sup>2</sup> = 1	I.71; Chi²	= 570.	67, df =	4 (P <	0.000			1.55 [0.35, 2.75]		
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1	I.71; Chi²	= 570.	67, df =	4 (P <	0.000			1.55 [0.35, 2.75]	-10 -5 0 5 10	
Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 Fest for overall effect: 2	1.71; Chi² Z = 2.52 (F	= 570. P = 0.0	67, df = 1)	,		01); l² =	= 99%	1.55 [0.35, 2.75]		n
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1	1.71; Chi² Z = 2.52 (F	= 570. P = 0.0	67, df = 1)	,		01); l² =	= 99%	1.55 [0.35, 2.75]	-10 -5 0 5 10 Favours [control] Favours [experimenta	ŋ

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other biases

FIGURE 21

Schirmer's test.

		erimen			Control			Mean Difference		Mean Differe		Risk of Bias
Study or Subgroup		SD	Total	Mean	SD	Total	Weight	IV, Random, 95% 0		IV, Random, 9	5% CI	ABCDEFG
.4.1 IGU+other ther	ару											
iang et al. 2021	24.01	3.24	30	27	3.51	30	9.0%	-2.99 [-4.70, -1.28]	]	-		
hao 2020	16.52	2.56	25	26.65	3.59	25	9.0%	-10.13 [-11.86, -8.40]	]			
huang 2020	17.28	4.06	34	26.21	5.32	34	8.8%	-8.93 [-11.18, -6.68]	]	•		??
/iu 2018	18.14	5.04	20	27.12	7.03	20	8.1%	-8.98 [-12.77, -5.19]	]			??+++++
Vang et al. 2019	15.94	8.25	32	19.73	5.04	32	8.3%	-3.79 [-7.14, -0.44]	]	-		
Chen et al. 2022	16.53	3.87	62	23.62	4.33	62	9.1%	-7.09 [-8.54, -5.64]	]	•		
u and Zhang 2021.	16.98		48	37.5	6.71	48	8.9%	-20.52 [-22.65, -18.39]	]	•		
lie et al. 2020	28.4	16.3	38	36.6	17.8	38	5.9%	-8.20 [-15.87, -0.53]				
iang et al. 2021	19.79		24		15.16	22	6.3%	-15.28 [-22.15, -8.41]				?? • • ? • •
ing et al. 2022	16.22			28.63	3.71	20		-12.41 [-14.49, -10.33]		•		??••••
iu 2022	16.16		40	22.53	5.42	40	8.8%	-6.37 [-8.57, -4.17		•		
Zhuang et al. 2021	17.02	2.14	10	19.4	2.65	10	8.9%	-2.38 [-4.49, -0.27	]	.1		?? 🗣 🗣 🗣 🗣
Subtotal (95% CI)			383			381	100.0%	-8.80 [-11.88, -5.72]		•		
.4.2 IGU only										_		
Ku et al. 2017	16.08	2.39	47	26.97	2.55	47	11.6%	-10.89 [-11.89, -9.89]	]	•		•?••+
uo et al. 2018.	16.17	7.25		20.73	6.94	40	9.9%	-4.56 [-7.67, -1.45	]	-		<b>??+++++</b>
Zhang et al. 2019	16.15		100	20.74	6.97	100	11.0%	-4.59 [-6.56, -2.62]		•		??
lia 2020	17	2.4	43	19.4	2.7	43	11.6%	-2.40 [-3.48, -1.32]		1		
Shao et al. 2020	26.4	12.2	26	30.6	18.8	19	4.1%	-4.20 [-13.87, 5.47				
′u 2020	16.24		38		3.17	38	11.5%	-5.10 [-6.37, -3.83				??+++++
ai et al. 2019	16.9	2.8	30	16.7	6.3	30	10.6%	0.20 [-2.27, 2.67]		Ť		• ? • • • • • •
Rao et al. 2022	16.18			21.28	3.21	43	11.5%	-5.10 [-6.32, -3.88				$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$ $\bullet$
i et al. 2018	16.36		34		8.27	34	9.5%	-6.32 [-9.87, -2.77]		•		
i et al. 2020	16.35	6.54		22.67	8.26	23	8.7%	-6.32 [-10.63, -2.01		T		<b>6 6 6 6 6 6</b>
Subtotal (95% CI)			424				100.0%	-4.97 [-7.41, -2.54]	1	•		
eterogeneity: Tau <sup>2</sup> =				(	P < 0.00	0001); I	² = 95%					
est for overall effect:	∠ = 4.00	) (P < (	0.0001)									
									-100	-50 0	50 100	
ant for each many - 100		01:2	0.05	- 1/5	- 0.000	12 - 7	0.00/		Favours	[experimental] Fav	ours [control]	
est for subgroup diff	erences:	Cni <sup>2</sup> =	3.65, 0	τ = 1 (P	= 0.06)	$ 1^{\circ} = 72$	2.6%					
Risk of bias legend		,										
A) Random sequenc				bias)								
B) Allocation concea	,		/									
C) Blinding of particip	pants and	perso	nnel (p	ertorma	nce bia	s)						

(C) binding of participants and personnel (performan (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other biases

#### FIGURE 22

Esr.

		erimen			ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup		SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
.5.1 IGU+other ther	ару									
/liu 2018		3.02		10.36		20	20.1%	-1.27 [-1.96, -0.59]	*	<b>? ? • • • • •</b>
(ie et al. 2020	3.6	1.3	38		1.5	38	21.0%	-0.14 [-0.59, 0.31]	1	<b></b>
iang et al. 2021.	7.08	1.02		11.02		30	19.4%	-3.61 [-4.45, -2.77]	*	
liang et al. 2021		2.02		1.12		22	20.5%	0.05 [-0.53, 0.63]	Ť	3 3
huang et al. 2021	12.07	2.34		14.81	3.16	10	19.0%	-0.94 [-1.88, -0.01]	1	?? 🖉 🖝 🛨 🛨
Subtotal (95% CI)			122				100.0%	-1.16 [-2.31, -0.00]	-	
leterogeneity: Tau <sup>2</sup> =				= 4 (P <	< 0.000	01); l²	= 93%			
est for overall effect	: Z = 1.97	(P = 0	.05)							
.5.2 IGU only										
liang et al. 2016	16.13	2.32	30	17.53	6.62	30	100.0%	-0.28 [-0.79, 0.23]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI)			30			30	100.0%	-0.28 [-0.79, 0.23]	•	
leterogeneity: Not ap	plicable									
est for overall effect	Z = 1.07	(P = 0)	.28)							
									-10 -5 0 5 10	—
								Fa	vours [experimental] Favours [control]	
est for subgroup diff	erences:	Chi² =	1.86, d	lf = 1 (P	= 0.17	),   <sup>2</sup> = 4	16.3%	10	vouis [experimental] T avouis [control]	
Risk of bias legend										
A) Random sequence	e generat	tion (se	election	bias)						
B) Allocation concea	Iment (se	lection	bias)							
C) Blinding of partici				erforma	nce bia	as)				
D) Blinding of outcom						,				
E) Incomplete outcor					, 					
F) Selective reporting										
G) Other biases	, ( p	3	,							
-,										
RE 23										

	Expo	eriment	al	C	Control			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% CI	ABCDEFG
1.6.1 IGU+other therapy	У									
Xia et al. 2017	18.44	2.31	50	23.97	3.46	50	10.8%	-5.53 [-6.68, -4.38]	-	??
Zhang and Shen 2019	19.4	3.55	43	24.76	4.11	43	10.2%	-5.36 [-6.98, -3.74]	-	• ? • • • • •
Zhao 2020	14.3	2.2	25	16.8	3	25	10.4%	-2.50 [-3.96, -1.04]	-	• ? • • • • •
Zhuang 2020	17.49	1.21	34	23.41	3.18	34	10.8%	-5.92 [-7.06, -4.78]	-	??
Wei 2019	15.4	3.7	30	19.8	4.2	30	9.7%	-4.40 [-6.40, -2.40]	-	?????+++
Wang et al. 2019	19.66	5.83	32	25.67	8.08	32	7.5%	-6.01 [-9.46, -2.56]		• ? • • • • •
Chen et al. 2022	19.44	4.02	62	28.37	7.42	62	9.6%	-8.93 [-11.03, -6.83]	-	• ? • • • •
Lu and Zhang 2021	14.37	3.51	48	39.97	24.33	48	3.7%	-25.60 [-32.55, -18.65]		• ? • • • • •
Ding et al. 2022	19.56	5.14	20	30.63	4.89	20	8.0%	-11.07 [-14.18, -7.96]	-	?? 🕈 🖶 🖶 🛨
Liu 2022	18.98	3.62	40	25.13	4.2	40	10.1%	-6.15 [-7.87, -4.43]	-	• ? • • • •
Zhuang et al. 2021	14.27	2.15	10	16.73	2.98	10	9.3%	-2.46 [-4.74, -0.18]	-	?? ? 🛑 🖶 🖶 🛨
Subtotal (95% CI)			394				100.0%	-6.44 [-8.05, -4.83]	♦	
Heterogeneity: Tau <sup>2</sup> = 5.1	93: Chi <sup>2</sup>	= 80.10	df = 1	0 (P < )	0.00001	): $ ^2 = 8$	88%			
Test for overall effect: Z				- (		,,				
1.6.2 IGU only										
Xu et al. 2017	18.66	5.83	47	22.64	6.08	47	10.2%	-3.98 [-6.39, -1.57]	-	
uo et al. 2018	18.62	5.84		22.67	6.05	40	9.7%	-4.05 [-6.66, -1.44]	-	??
lia 2020	18.26	3.78		25.23	4.32	43		-6.97 [-8.69, -5.25]	-	
liang et al. 2016	18.42	2.03		20.22	4.78	30	11.3%	-1.80 [-3.66, 0.06]	-	
/u 2020	17.58	1.14		23.39	3.26	38	12.7%	-5.81 [-6.91, -4.71]	•	7744444
Rao et al. 2022	17.72	3.42		23.64	3.28	43		-5.92 [-7.34, -4.50]	-	
Bai et al. 2019	19	3.42	30	20.04	4	30		-1.00 [-2.79, 0.79]	-	
Gu 2020	58.02			71.91		40	1.8%	-13.89 [-24.55, -3.23]		
_i et al. 2020	18.36	5.36	23	25.6	7.92	23	7.2%	-7.24 [-11.15, -3.33]		??
Zhao 2019	18.31		41		4.89	41	11.8%	-2.26 [-3.88, -0.64]	-	<b>A?AAAAA</b>
Subtotal (95% CI)	10.01	2.01	375	20.07	4.05		100.0%	-4.42 [-5.94, -2.90]	•	
Heterogeneity: Tau <sup>2</sup> = 4.4	41. Chi2	= 52.62		A/P < 0	00001)					
Test for overall effect: Z				(1 - 0.		, 1 - 00	,,,,			
	(									
								-	-20 -10 0 10 20	_
								Fa	vours [experimental] Favours [control]	
Test for subgroup differe	nces: Ch	hi² = 3.2	:0, df =	1 (P = (	0.07), l <sup>2</sup>	= 68.8	%	14		
Risk of bias legend										
A) Random sequence g	eneratio	n (selec	tion bia	as)						
B) Allocation concealme	ent (sele	ction bia	as)							
C) Blinding of participan	ts and p	ersonne	el (perfo	ormance	e bias)					
c) binding of participan	assessm	ient (det	tection	bias)						
		rition bia	as)							
D) Blinding of outcome a	data (att									
<ul> <li>(D) Blinding of participant</li> <li>(D) Blinding of outcome a</li> <li>(E) Incomplete outcome</li> <li>(F) Selective reporting (re</li> </ul>	•	bias)								
(D) Blinding of outcome a (E) Incomplete outcome	•	bias)								
<ul> <li>(D) Blinding of outcome a</li> <li>(E) Incomplete outcome</li> <li>(F) Selective reporting (reg)</li> <li>(G) Other biases</li> </ul>	•	bias)								
<ul> <li>D) Blinding of outcome a</li> <li>E) Incomplete outcome</li> <li>F) Selective reporting (re</li> </ul>	•	bias)								

# 4.3 IGU for PSS

The pathogenesis of PSS is complex and has not yet been clearly studied. At present, it is believed that it may be related to various factors such as genetics, environment, endocrine, and immune abnormalities (Fasano et al., 2020a; Huang et al., 2021). Among them, the excessive activation of B cells produces a variety of autoantibodies and hyperimmunoglobulinemia plays an important role in the development of pSS. In this process, T cells also participate in the maturation and differentiation of B cells by secreting a variety of cytokines (Rivière et al., 2020). More than 80% of patients with Sjögren's syndrome will experience symptoms of dryness, fatigue and joint pain, which will affect the patient's work efficiency and reduce the patient's quality of life (Marshall and Stevens, 2018). However, there is currently no specific drug for the treatment of pSS. Therefore, exploratory research on PSS therapeutic drugs is currently underway (Carsons et al., 2017; Vehof et al., 2020). As a new type of DMARD, IGU's main mechanism of action is highly compatible with the complex pathogenesis of SS, and has therapeutic potential. A number of clinical studies have shown that IGU can effectively improve the disease activity (such as ESSDAI), various serum indicators (IgG, IgM, IgA, ESR, RF) and lacrimal gland secretion function (detected by Schirmer I test) in patients with pSS.

This meta-analysis also showed that IGU can reduce the ESSPRI score and ESSDAI score, inhibit the inflammation factors (reduce ESR, CRP and RF) and increase Schirmer's test score. The incidence of adverse events in IGU group was also lower than that in control group, indicating that the addition of IGU may be an effective and safe treatment plan. In addition, the dose of IGU in all RCTs was 50 mg (25 mg Bid for most RCTs and 50 mg Qd for a few RCTs), suggesting that IGU at this dose had a good effect on PSS without increasing the incidence of adverse events. B cell hyperactivity is a key pathogenic factor in pSS, which is mainly characterized by the formation of ectopic germinal centers in the lacrimal and salivary glands (Carsons et al., 2017; Fasano et al., 2020b; Du W. et al., 2021). Therefore, reducing B cell activity and suppressing immunoglobulin production have become the key to treatment. Studies have shown that IGU not only inhibits the proliferation of T cells, but also inhibits the differentiation of antibody secreting cells (ASCs) in RA patients by activating the PKC/EGR1 pathway, thereby regulating the immune response of B cell differentiation and relieving clinical symptoms (Ye et al., 2019a). However, whether IGU can play a role in the treatment of pSS patients by inhibiting the activity of B cells has not yet been determined.

	Experime		Contro			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
.7.1 IGU+other therapy								
/liu 2018	2	20	2	20	3.1%	1.00 [0.16, 6.42]		??+++++
Vang et al. 2019	4	32	3	32	4.7%	1.33 [0.32, 5.49]		
Zhao 2019	2	41	3	41	4.7%	0.67 [0.12, 3.78]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
Kie et al. 2020	7	38	5	38	7.8%	1.40 [0.49, 4.02]	_ <del></del>	$\bullet ? \bullet \bullet \bullet \bullet \bullet$
hang and Shen 2019	7	43	6	43	9.4%	1.17 [0.43, 3.19]	_ <del>_</del> _	• ? • • • • •
iang et al. 2021	5	30	4	30	6.2%	1.25 [0.37, 4.21]	<b>-</b> _	• ? • • • • •
Zhao 2020	4	25	5	25	7.8%	0.80 [0.24, 2.64]		• ? • • • • •
Vei 2019	4	30	9	30	14.1%	0.44 [0.15, 1.29]		?????+++
u and Zhang 2021	14	48	13	48	20.3%	1.08 [0.57, 2.04]	_ <b>+</b> _	• ? • • • • •
liang et al. 2021	1	24	1	22	1.6%	0.92 [0.06, 13.79]		?? 🗣 🗣 ? 🖶 🛨
Ding et al. 2022	3	20	2	20	3.1%	1.50 [0.28, 8.04]	<del></del>	?? 🕈 🖶 🖶 🛨
iu 2022	4	40	5	40	7.8%	0.80 [0.23, 2.76]		
Zhuang et al. 2021	3	10	6	10	9.4%	0.50 [0.17, 1.46]		??
Subtotal (95% CI)	5	401	5		100.0%	0.94 [0.68, 1.29]	<b></b>	
Total events	60		64				1	
leterogeneity: Chi <sup>2</sup> = 5.1		(P = 0.9)						
Test for overall effect: Z			, i = 0 /					
1.7.2 IGU only								
liang et al. 2020	3	25	5	25	6.6%	0.60 [0.16, 2.25]		??
Shao et al. 2020	6	44	1	22	1.8%	3.00 [0.38, 23.40]		
liang et al. 2016	1	30	1	30	1.3%	1.00 [0.07, 15.26]		• ? • • • • •
liang et al. 2014	4	25	5	25	6.6%	0.80 [0.24, 2.64]		??
Bai et al. 2019	3	30	11	30	14.6%	0.27 [0.08, 0.88]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
Gu 2020	2	40	8	40	10.6%	0.25 [0.06, 1.11]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
i et al. 2018	9	34	10	34	13.3%	0.90 [0.42, 1.93]		
i et al. 2020	3	23	10	23	13.3%	0.30 [0.09, 0.95]		?? 🗣 🗣 🗣 🗣
uo et al. 2018	7	40	9	40	11.9%	0.78 [0.32, 1.88]		??
Zhang et al. 2019	5	100	3	100	4.0%	1.67 [0.41, 6.79]	- <del>  -</del>	?? 🗣 🗣 🗣 🗣
lia 2020	7	43	9	43	11.9%	0.78 [0.32, 1.90]		
Gu 2022	2	42	3	42	4.0%	0.67 [0.12, 3.79]		• ? 🖶 🖶 🗣 🗣
Subtotal (95% CI)		476		454	100.0%	0.66 [0.48, 0.92]	•	
Total events	52		75					
Heterogeneity: Chi <sup>2</sup> = 10	.47, df = 11	(P = 0.4	49); l² = 0	%				
lest for overall effect: Z	= 2.45 (P =	0.01)						
						0.005	5 0.1 1 10	200
Toot for out group differen	Deser OF 12	- 0.10	K - 1 (D -	0.14	12 - 54 04	Favours	[experimental] Favours [control	
Test for subgroup differe	nces: Chi*	- 2.18, 0	л = т (Р =	0.14)	, 1 = 54.2	70		
Risk of bias legend			h la ch					
A) Random sequence g			i bias)					
B) Allocation concealme		,						
C) Blinding of participan				ce bia	s)			
D) Blinding of outcome a			ion bias)					
E) Incomplete outcome	,	,						
F) Selective reporting (re	eporting bia	as)						
G) Other biases								
RE 25								
rse events.								

# 4.4 IGU for interstitial pneumonia

Early symptoms of RA-interstitial pneumonia (RA-ILD) are often atypical and easy to miss (Chernau et al., 2019; Graney and Fischer, 2019). At present, there is no targeted treatment for RA-ILD, and two clinical strategies are mainly used: anti-inflammatory and anti-fibrosis. In terms of anti-inflammatory, the dosage and treatment time of hormones and immunosuppressants are difficult to grasp. Excessive immunosuppression can also lead to secondary infection aggravating the disease. Therefore, clinical studies are still searching for safe and effective therapeutic drugs for RA-ILD (Wells and Denton, 2014; Santhanam et al., 2020). The current study shows that the potential mechanisms of IGU treatment of pulmonary fibrosis include: inhibition of inflammation and epithelial-mesenchymal transition (EMT) process (Luppi et al., 2020). For example, Luo et al. found that inflammatory cell infiltration, inflammatory factor and chemokine expression in the lung tissue of mice treated with IGU treated mice with idiopathic pulmonary fibrosis decreased in a dose-dependent manner. This suggests that IGU can inhibit the pulmonary inflammatory response that accompanies the process of pulmonary fibrosis (Yoo et al., 2020). Zhao et al. found that high doses of IGU and methylprednisolone had inhibitory effects on alveolitis and pulmonary fibrosis in a bleomycin-induced mouse model of pulmonary fibrosis (England and Hershberger, 2020). Zhu et al. found that IGU can inhibit TGF- $\beta$ 1-mediated human lung fibroblast activation and collagen secretion through the Smad3/p300 pathway, and it may be an effective anti-fibrotic drug to delay the progression of PF (Kadura and Raghu, 2021).

In this systematic review and meta-analysis, Zhuang et al. (2021) and Zhang et al. (2019) reported the treatment of PSS with interstitial pneumonia. DongZhang et al. (2019) reported the treatment of RA with interstitial pneumonia. The meta-analysis results showed that FVC increased after IGU treatment. Meanwhile, Zhuang et al. (2021) showed

· · ·	-		-			
Outcomes	Illustrative c	omparative risks* (95% Cl)	Relative effect	No of participants (studies)	Quality of the evidence	Comments
	Assumed risk	Corresponding risk	(95% CI)		(GRADE)	
	Control	Primary outcomes				
ESSPRI - IGU + other therapy		The mean ESSPRI in the intervention groups was 1.71 lower (2.44–0.98 lower)		500 (7 studies)	⊕⊕⊙⊙ low <sup>a,b</sup>	
ESSDAI - IGU + other therapy		The mean ESSDAI in the intervention groups was 1.62 lower (2.3–0.94 lower)		620 (8 studies)	⊕⊕⊙⊙ low <sup>a,b</sup>	
Schirmer's test - IGU + other therapy		The mean Schirmer's test in the intervention groups was 2.18 higher (1.76-2.59 higher)		466 (6 studies)	⊕⊕⇔⊃ low <sup>a,b</sup>	
Advers events - IGU +	Study population	1	RR 0.94	800 (13 studies)	⊕⊕⊕⊙ moderateª	
other therapy	160 per 1,000	151 per 1,000 (109–207)	- (0.68–1.29)	(15 studies)	moderate	
	Moderate	·				
	132 per 1,000	124 per 1,000 (90-170)				

#### TABLE 5 Evidence quality of IGU for PSS in IGU + other therapy subgroup.

<sup>a</sup>Downgraded one level due to serious risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcomes) and most of the data comes from the RCTs, with moderate risk of bias.

<sup>b</sup>Downgraded one level due to the probably substantial heterogeneity.

#### TABLE 6 Evidence quality of IGU for PSS in IGU only subgroup.

Outcomes	Illustrative c	omparative risks* (95% Cl)	Relative effect (95% Cl)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Adverse event				
ESSPRI - IGU only		The mean ESSPRI in the intervention groups was 2.1 lower (2.4–1.81 lower)		583 (9 studies)	$\bigoplus \Theta \Theta \Theta$ very low <sup>a,b,c</sup>	
ESSDAI - IGU only		The mean ESSDAI in the intervention groups was 1.51 lower (1.65–1.37 lower)		385 (6 studies)	⊕⊕⊕⊙ moderate <sup>a</sup>	
Schirmer's test - IGU only		The mean schirmer's test in the intervention groups was 1.55 higher (0.35-2.75 higher)		325 (5 studies)	⊕⊕⊝⊝ low <sup>a,b</sup>	
Adverse events -	Study population	n	RR 0.66 (0.48–0.92)	930 (12 du line)	⊕⊕⊕⊙ moderateª	
IGU only	165 per 1,000	109 per 1,000 (79–152)		(12 studies)	moderate"	
	Moderate		-			
	200 per 1,000	132 per 1,000 (96–184)				

\*Downgraded one level due to serious risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcomes) and most of the data comes from the RCTs, with moderate risk of bias.

<sup>b</sup>Downgraded one level due to the probably substantial heterogeneity.

<sup>c</sup>Downgraded one level due to potential publication bias.



#### FIGURE 26

Summary of the mechanism of IGU treatment of rheumatic and autoimmune diseases (IGU may regulate immune cell function and activity to balance immune cell subsets, thereby further reducing inflammation and tissue damage. pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; OA, Osteoarthritis; SLE, systemic lupus erythematosus; AS, ankylosing spondylitis; LN, lupus nephritis; CTD-ILD, connective tissue disease associated interstitial lung disease).

that both DLCO and 6MWT improved in both groups after treatment, and the degree of improvement in 6MWT in the IGU group was due to that in the control group. Zhang et al. (2019) reported that MMF was also improved after treatment, and the improvement was greater in the IGU group than in the control group. DongZhang et al. (2019) showed that compared with the control group, both FEV1 and TLC were improved after IGU treatment. These all suggest the therapeutic effect of IGU on autoimmune diseases complicated with interstitial pneumonia. In terms of economics and drug insurance policy, IGU is a relatively inexpensive drug that is available in most countries. A real-world study retrospectively analyzed the population characteristics, efficacy and influencing factors of RA patients who received IGU treatment for at least 6 months between July 2015 and October 2020 and had more than 3 follow-up records. The results showed that IGU was well tolerated and an effective treatment drug, which is a treatment option for RA patients with interstitial lung disease.

# 4.5 IGU for other rheumatic and autoimmune diseases

SLE is an autoimmune inflammatory disease that affects multiple organs and connective tissues. It is more common in young women and is seeing an increase in early, mild, and atypical cases (Luo et al., 2015; Shao et al., 2021). Within 5 years, most SLE patients will develop LN, which remains a significant cause of morbidity and mortality (Zhao et al., 2017b). While several drugs have demonstrated efficacy in treating the disease, 20%–35% of LN patients experience relapse or treatment failure, and drug intolerance is a frequent issue (Fu et al., 2021). In preclinical studies with lupus, IGU prevented autoimmune nephritis, reduced proteinuria, and decreased immune complex deposition in MRL/lpr mice (Anders et al., 2020). As the most critical pathogenic cells in the progression and development of systemic

lupus erythematosus, B cells are closely related to the systemic damage and antibody secretion of SLE (Gasparotto et al., 2020; Ayoub and Nachman, 2021). The earliest study on the mechanism of IGU on B cell differentiation found that it can inhibit the production of immunoglobulin by B cells (Mahajan et al., 2020). In a phase III clinical trial in RA, IGU reduced serum immunoglobulin concentrations (Yan et al., 2014; Canny and Jackson, 2021). In animal models of RA and lupus, IGU reduced autoantibody titers, including anti-collagen antibodies (Tanaka et al., 2003; Ma et al., 2019) and anti-double-stranded (dsDNA) antibodies [198]. Interestingly, IGU has been reported to reduce peripheral plasma cell counts without affecting the total B cell population in MRL/lpr mice (Anders et al., 2020). Further studies have shown that in RA patients receiving IGU only, IGU regulates key transcription factors affecting plasma cell differentiation through the PKC/Egr1 axis, especially Blimp-1 (Hara et al., 2007). A recent observational study found that more than 90% of patients with refractory LN responded to IGU within 24 weeks without the need to increase steroid dosage or add any other drugs during follow-up (Lu et al., 2009). Yan et al. are currently conducting a multicenter, randomized, 52-week parallel active drug-controlled study (Du et al., 2008). The study aims to investigate the efficacy of iguratimod as first-line treatment for patients with LN. Patients with biopsy-proven active lupus nephritis from six study sites in China were randomly assigned to the experimental or control group. During the first 24 weeks, IGU was compared to cyclophosphamide as induction therapy, while during the second 24 weeks, IGU was compared to azathioprine as maintenance therapy. The primary outcome was the rate of renal response, including complete and partial response at week 52, which will be analyzed using a noninferiority hypothesis test. This ongoing trial will determine whether iguratimod can be used as an alternative induction or maintenance therapy for lupus nephritis patients (Du et al., 2008).

In summary, the mechanism of IGU treatment of rheumatic and autoimmune diseases is summarized in Figure 26.

# 4.6 Strengths and limitations

Compared with previous systematic reviews and meta-analyses, the strengths of this study are: 1) Compared with previous studies on PSS (Luo et al., 2013; Pu et al., 2021), this study included newer and more RCTs (32, 5 of which were published in 2022), and the quality of evidence was assessed. 2) Compared with previous studies on RA (Ye et al., 2019b; Kang et al., 2020; Shrestha et al., 2020; Hu et al., 2021; Shrestha et al., 2021; Yan et al., 2021; Zeng et al., 2022a; Zeng et al., 2022b; Long et al., 2023), this study also included newer and more RCTs (43, 4 of which were published in 2022); and the intervention in the IGU group is IGU alone or IGU combined with other drugs, not limited to IGU + MTX, and further found that the combination of IGU + MTX may reduce the occurrence of adverse events, while IGU combined with other drugs only does not increase adverse events. 3) Compared with previous studies on AS (Chen et al., 2021; Liu B. et al., 2021; Deng et al., 2022; Ouyang et al., 2022; Long et al., 2023), this research employed a more rigorous screening process for RCTs. Moreover, this systematic review and meta-analysis integrated findings from various rheumatic and autoimmune diseases. As a result, the efficacy of IGU treatment for AS can be cross-compared with the outcomes of IGU treatment for other rheumatic and autoimmune diseases. 4) This study also evaluated the efficacy and safety of IGU in the treatment of autoimmune disease with interstitial pneumonia for the first time. 5) This study performed a thorough search of different databases and included Chinese databases.

The limitations include: 1) Although there is no language restriction, most of the included RCTs are in Chinese and English, and no literature in other languages has been found, so there may be publication bias. 2) The basic treatment, course of treatment, and observation time of the indicators are also different, and the clinical heterogeneity among the subgroups is high, which leads to a decrease in the accuracy and implementability of the results. 3) Although 84 RCTs were included, only 4 types of diseases (RA, AS, PSS and Autoimmune disease with interstitial pneumonia) were involved, and RCTs of IGU for other rheumatic and autoimmune diseases were not retrieved. 4) Since RCTs did not report on patients' disease conditions in detail (such as naive RA and MTX-resistant RA), subgroup analysis of patients' disease conditions could not be performed. 5) The RCTs included in this study are all in English or Chinese, and there are no literature in other languages (such as Japanese) for the time being, which may lead to potential bias. 6) The quality of evidence for most outcomes was assessed as low to very low, which may affect the generalization of conclusions.

Based on these shortcomings, more IGUs are needed in the future for RCTs of other rheumatic and autoimmune diseases

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(such as SLE). Furthermore, future RCTs are expected to report more detailed patient medication information to facilitate subgroup analysis and reduce clinical heterogeneity.

# 5 Conclusion

Based on current evidence, IGU may be a safe and effective for the treatment of RA, AS, PSS and autoimmune diseases with interstitial pneumonia. The quality of evidence was very low to moderate. The recommended dose is 25–50 mg. However, more RCTs about other type of rheumatic and autoimmune diseases are still needed.

# Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

# Author contributions

LZ and KY are responsible for the study concept and design. LZ, QH, YD, YL, JC, YL, AG, KY, XZ, ZL, and LS are responsible for the data collection, data analysis and interpretation; LZ and KY drafted the paper; LS supervised the study. All authors contributed to the article and approved the submitted version.

# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1189142/ full#supplementary-material

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