infusion and has a terminal half-life of 8 to 10 days. Hence it is administered every 4 to 8 weeks and the dosage lies between 3 to 5 (to 10) mg/kg.

The efficacy of infliximab with MTX has been demonstrated in several trials (Table1). Patients receiving combination therapy achieved obviously higher median improvements in ACR-N than those in the MTX plus placebo group [16-18]. In addition, the clinical efficacy is similar in different dosage of infliximab group [16-18]. In terms of radiographic image, the combination of infliximab and MTX prevented the radiographic progression and led to lasting clinical amelioration [16]. Infliximab treatment inhibited progression of joint damage even in patients take low of MTX in the RISING study [18]. Compared with the MTX-only-treated patients, both erosions and joint space narrowing obviously reduced from baseline in the infliximab plus MTX-treated patients except infliximab 3 mg/kg every 8 weeks. There were fewer newly eroded joints per patient in the infliximab plus MTX treatment groups than in the MTX-only group [17]. The studies by St Clair EW illustrated that HAQ scores accelerated more in the group conducted infliximab than in the group receiving MTX alone [16].

The most common adverse events found in clinical trials of infliximab included infusion reactions, infection. The therapy of infliximab might increase the risk of malignancies tumors and cardiovascular [19]. The incidence of serious infections, acute infusion reactions, and death was similar between patients treated with infliximab plus MTX and those adopted MTX only [17]. Among the serious infections, pneumonia, tuberculosis occurred more frequently in the infliximab-treated patients than in those treated with MTX alone [16,19].

Etanercept is a genetically engineered protein consisting of two molecules of the extracellular domain of TNF receptor II (p75) and the Fc portion of IgG1 [20]. Owe to its half-life of approximately 3-5.5 days, etanercept is administered subcutaneously (s. c) either weekly (50mg) or twice a week (25mg) [21].

The superiority of the combination therapy of etanercept plus MTX over etanercept or MTX monotherapy in patients with RA has been demonstrated (Table 2) [22-24]. The 2-year data from the TEMPO study confirmed that apparently larger proportion of patients treated with combination therapy achieved the clinical response than that receiving either monotherapy [22]. Moreover, the combination-treated patients had predominantly lower erosion change scores (-0.67) than patients treated with etanercept alone (0.39) or MTX alone (3.25) [25]. Therefore, treatment with a combination of etanercept and MTX halted joint damage and patients achieved disease remission [25]. Sustained efficacy and decreased rate of radiographic progression gained in patients with early aggressive RA who use long-term treatment with etanercept [26]. Patients adopted combination therapy enhanced greatly in function status than in group of monotherapy [27]. Additionaly, etanercept 50 mg once weekly is an optimal in most patients with RA. Increasing the dosage of etanercept from 50mg once a week to 50 mg twice a week in suboptimal responders did not dramatically improve response rates [28]. There was no obvious improvement between etanercept as monotherapy at 50 mg twice weekly and 25 mg twice weekly with regard to the safety and efficacy [29].

Injection-site reactions and hypertension were more common with etanercept than with MTX or with combination therapy [22]. These events were mostly mild or moderate. Nausea and vomiting were more often concerned with MTX than with etanercept or combination therapy. No significant differences were seen among the groups in the incidence of serious adverse events (infectious and noninfectious) [22].

In summary, etanercept was benefit for patients with RA. But the combination of etanercept with MTX is superior to a montherapy with each drug. The combination regimen can reduce disease activity, slow radiographic progression and improve function. Furthermore, the treatment with etanercept plus MTX was well-tolerated and did not increase serious adverse events.

Adalimumab is a monoclonal antibody of recombinant immunoglobulin (IgG1) containing only human sequences of peptides. It is an antagonist of TNF, which prevent the binding of TNF-α to its receptors [6]. It has a half-life of 10–20 days and can be used as monotherapy or in combination with several other DMARDs, preferably MTX [30,31]. The recommended dose of adalimumab is 25 mg s. c twice a week.

Treatment with adalimumab plus MTX was found to be statistically superior to placebo plus MTX according to the ACR20/50/70 response rates at week 26 (Table 3) [32]. If patients received

First author		Disease	ACR20	ACR50	ACR70	
St.Clair EW et al. [16]			62.4 66.2 53.6	45.6 50.4 32.1	32.5 37.2 21.2	0.4 ± 5.8 0.5 ± 5.6 3.7 ± 9.6
al. [17]			42 40 48 40 16	21 30 36 20 6	10 21 20 10 1	1.02 ± 7.13 1.03 ± 11.65 1.14 ± 4.92 -0.42 ± 6.10 12.59 ± 20.05
et al. [18]			75.8 78.8 82.7	60.6 58.7 66.3	37.4 42.3 43.3	

Table1:

First author		Disease Duration	ACR20	ACR50	ACR70	DAS28 <2.6(%)	TTS (mean)
et al. [22]	ETN		86 75 71	71 54 42	49 27 21	42.4 22.4 18.9	-0.56 1.10 3.34
et al. [23]	ETN ETN		 81,0 70.8 62.2	 83.8 88.5 50.0	 82.6 66.7 63.2		-1.35 -0.19 2.82
et al. [24]	ETN		90.4 63.8	64.4 47.8	38.4 26.1	27.4 10.1	

Table 2:

adalimumab+MTX in early RA, they would achieve rapid clinical and functional improvements [32]. Adalimumab regimens decreased risk of radiographic disease progression [33]. In an open-label extension study of 5 years, the addition of adalimumab led to greater inhibition of structural damage compared with patients who continued with MTX monotherapy (Table 3) [34]. The PREMIESR study confirmed that treatment with adalimumab plus MTX is initiated early, it contribute to higher improvements in clinical, functional, and radiographic responses as compared with the treatment with MTX alone or adalimumab alone [35].

In addition, adlimumab plus MTX ameliorated physical function for patients with RA [33,36].

Adalimumab had good tolerance generally. The research demonstrated that the rate of adverse events (both serious and nonserious) was similar in the adalimumab and placebo groups, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than that in placebo (0.5%) ($P<0.02$), and was the highest in the patients adopted 40mg every other week [33]. The common adverse events were injection site reactions, serious infections such as military tuberculosis, cellulitis [35]. However, adalimumab were safe and well tolerated. These adverse events were not serious and severe side effects were relatively seldom.

Golimumab is a human anti-TNF-α monoclonal antibody that was generated and affinity matured in an in-vivo system [37]. Golimumab has a high affinity and specificity for human TNF-α and effectively neutralizes TNF-α bioactivity in vitro [38].

The efficacy of golimumab had been testified in several different groups (Table 4) [37,39,40]. The combination of golimumab and MTX was significantly better at improving the signs and symptoms of RA and physical funcion [37]. The differece weren't observed in the efficacy of the two golimumab dose group (50 mg and 100 mg) [37]. Though compared individually with the pacebo group, the golimumab in combination with MTX in patients with RA showed greater clinical response , the response rates did not displayed a clear dose-response pattern among the group of golimumab plus MTX (Table 4) [39].

In the multicenter, randomized, placebo-controlled GO-FORWARD study, mean improvement from baseline in HAQ-DI was significantly greater for golimumab 50mg+MTX and 100mg+MTX versus placebo+MTX [41]. On the other hand, golimumab+MTX also elicited a significant better response than placeo+MTX in other efficacy parameters, including disease activity score (DAS28) response. And the combination of golimumab and MTX limit radiographic progression [42].

The safety of golimumab has been demonstrated in different trials. However, adverse events were reported in the process of treatment. The most frequent adverse events in the combined golimumab groups were nausea, headache, and injection sit reaction. Most events were mild or moderate in severity [43].

In general, golimumab, in combination with MTX, can alleviate the signs and symptoms of RA and improve physical function.

Certolizumab pegol is a humanized anti-TNF-αantibody with high affinity to TNF [44]. In managing patients with RA, the recommended dose of certolizumab pegol is 400 mg (given as two subcutaneous injections of 200 mg) initially and at week 2 and 4, followed by 200 mg every other week.

An international, multicentre, phase 3, randomized, double-blind, placebo-controlled study has assessed the efficacy of certolizumab pegol in MTX non-responders [45]. Compared to placebo treatment, certolizumab pegol plus MTX effectively reduced the signs and symptoms of RA, and inhibited progression of joint damage (Table 5) [45-46] .There were no obvious differences in clinical efficacy

idea of the therapy on RA. Biological agents can quickly relieve clinical symptoms and delay the bone destruction. When the TNF-α inhibitors apply to clinical practice, the combinations with DMARDs are conducive to ease the symptoms and prevent the bone structural damage and elevate physical function. Besides, the conversion between different agents BesComs elevate c agents BesComs elevr

65: 328-334.

28.

Arthritis Rheum 58: 1921-1930.

29.

30.

Ann Rheum Dis 63: 508-516.

31.

32.

976-986.

60.

61.

62.

arthritis. J Rheumatol 31: 1098-1102.

63.