Fusion proteins of biologic agents in the treatment of rheumatoid arthritis (RA)

A network meta-analysis

Mingcai Wu, MD[a], Mengjun Tao, MD[b], Quanhai Wang, MD[a], Xiaohua Lu, MD[c], Hui Yuan, MD, PhD[b,*] [iD]

Abstract

Background: To evaluate the efficacy of fusion proteins biologics (Etanercept (ETN), Anakinra (ANA), and Abatacept) combinations in the treatment of rheumatoid arthritis (RA) using network meta-analysis to rank those according to their performance medicines. The performance of these processes is ranked according to the results of the analysis and an explanatory study of the possible results is carried out.

Methods: Multiple databases including PubMed, EMBASE, and Cochrane Library were used to identify applicable articles and collect relevant data to analyze using STATA (14.0) software. The literature included in this study was divided into a combination of a placebo, methotrexate (MTX), and an observation group (1 of the 3 drugs). The last search date was December 12, 2019.

Results: A total of 19 eligible randomized controlled trials of fusion proteins biologics were identified, a total of 1109 papers were included, and the results showed that the ETN + MTX had the highest probability of being the most clinically efficacious intervention, with a surface under the cumulative ranking curve of 91.6, was significantly superior ($P < .05$). Patients who had received ETN or ETN + MTX or ANA had effective compared with patients who had received placebo (95% CI 1.28%–8.47%; 1.92%–19.18%; 1.06%–10.45%).

Conclusions: 1. The combination of ETN and MTX had the highest probability of optimal treatment compared to other drugs and 2. ENT, ENT + MTX, and ANA were effective in the treatment of RA compared to placebo.

Abbreviations: ABA = abatacept, ACR = American College of Rheumatology, ANA = anakinra, APC = antigen presenting cells, CI = confidence interval, ETN = etanercept, MTX = methotrexate, NMA = network meta-analysis, PrI = predictive interval, RA = rheumatoid arthritis, RCT = randomized controlled trial, SUCRA = surface values under the cumulative ranking, TNF = tumor necrosis factor.

Keywords: abatacept, anakinra, biologic agents, etanercept, meta-analysis, rheumatoid arthritis

[a] Department of Biochemistry and Molecular Biology, [b] Department of Epidemiology and Biostatistics, [c] Functional experiment and training center, School of Public Health, Wannan Medical College, Wuhu, China.

* Correspondence: Hui Yuan, Department of Epidemiology and Biostatistics, School of Public Health, Wannan Medical College, No. 22, Wenchang West Road, Yijiang District, Wuhu 241002, Anhui, China (e-mail: yuanhui0553@126.com).

1. Introduction

Rheumatoid arthritis (RA) is a dynamic process with systemic autoimmune disease characterized by synovial inflammation, which is influenced by factors such as genetic, environmental, and hormonal factors.[1] Recent studies have known that the key factor in destroying RA is the synovial fibroblasts in the hyperplastic synovial intima.[2] A series of events, including pain and joint destruction, are caused by the progressive inflammation of synovial joints.[3,4] The physical function and quality of life in RA patients are seriously threatened by joint destruction.[5] This disease frequently occurs among women than men, which affects about 1% of the population with 25 to 50 new cases occur annually in a population of 100,000.[6,7] Almost all RA patients need to be treated to delay or stop the development of the disease, or/and control the disease performance and reduce the disease burden.[8] RA treated by biological agents has the characteristics of better symptom control and disease alleviation, compared with traditional medicines such as methotrexate (MTX).[9] The currently available biological agents for RA can be classified as fusion proteins and monoclonal antibodies.[10] The fusion proteins are composed of a receptor portion of the target molecule and the Fc region of the immunoglobulin.[11] The currently available fusion proteins include Etanercept (ETN), Anakinra (ANA), and Abatacept (ABA). A series of studies have

shown that single-agent and combination medicines have an efficient effect on RA, but the best optimal treatment for the fusion protein of RA is still unknown. Therefore, it is necessary to explore the biological effects of fusion protein drugs for the treatment of RA, and the effect of different fusion protein combinations in the treatment of RA, for providing a theoretical basis for the treatment of RA with biological therapy. It is necessary to explore the effects of different fusion protein combinations on the treatment of RA, for providing a theoretical basis for the biological treatment of RA.

Network meta-analysis (NMA) is an upgraded version of the traditional meta-analysis.[12] It can comprehensively evaluate and classify multiple interventions simultaneously, especially in comparison with the effects of indirect different interventions using indirect controls. The aim of this study was to evaluate the efficacy of fusion proteins combinations in the treatment of RA using NMA to rank those according to their performance medicines (placebo, MTX, ETN, placebo + ETN, placebo + ANA, ANA + MTX, ABA + MTX, and ETN + MTX). It can identify the best way to treat RA with fusion proteins and help us understand the effective mechanism of disease treatment.

2. Methods

2.1. Search strategy

The databases used for this study included Pubmed, EMBASE, and Cochrane Library, which were searched before December 12, 2019, use Etanercept or Anakinra or Abatacept and rheumatoid arthritis with titles. By screening the titles and abstracts to ascertain whether the studies were met predefined selection criteria. Two reviewers screened the title and abstract of the paper as well as the potential related full-text articles. Then the data were extracted from the selected studies, including study characteristics, patient characteristics, and outcomes.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follow: (a) randomized controlled trials (RCTs); (b) all treatments or combinations can only be placebo or MTX or fusion proteins; (c) all patients with RA who met American College of Rheumatology (ACR) criteria for RA.[13]; (d) efficacy evaluation indicators were assessed using ACR20% (ACR20); (e) the language is English; and (f) multiple time nodes are taken only once for nearly 1 year.

The exclusion criteria were as follows: (a) biosimilar in RA; (b) other medications or combinations e) cost-effectiveness and cost-benefit evaluations; (c) case reports, systematic reviews; (d) animal experiments, cross-experimental studies; and (e) comparison before and after drug treatment, or no data available for analysis.

2.3. Efficacy evaluation criteria

Outcome indicators were included ACR 20 that defined as an improvement of 20% or more from baseline, in 3 of the following 5 domains: (a) a comprehensive assessment of arthritis activity by the patient; (b) a comprehensive assessment of arthritis activity by doctors; (c) patient assessment of arthritis pain. The assessment also included the number of joints (analysis from 66 joints) and the joint swelling (analysis from 68 joints); (d) health assessment questionnaire score; and (e) inflammatory markers, such as erythrocyte sedimentation rate or C-reactive protein.[14] An

ACR20% is defined as a 20% improvement in tender and swollen joint counts and the same level of improvement in 3 of the 5 domains.

2.4. Data extraction and quality evaluation

Literature and extraction were performed independently by 2 reviewers, based on the inclusion and exclusion criteria, including the following: (a) characteristics of the publication; (b) data quality of the publication; and (c) result indicator selection. The quality of the publications was evaluated using the Jadad quality scoring standard. Jadad scoring scale was consists of 3 items pertaining to descriptions of randomization, masking, and dropouts, and withdrawals in the report of an RCT. The scale ranges from 0 to 5, with higher scores indicating better reporting. High-quality trials scored more than 2 out of a maximum possible score of 5.[15]

2.5. Statistical analysis

Using commands of the network package in stata (14.0), the network, evidence contribution, predictive interval (*PrI*), funnel, and ranking plots were constructed. The efficacy of the intervention was ranked based on the surface values under the cumulative ranking (SUCRA) curve. The selected indicator was the count data, and *OR* is used as the combined effect, with a confidence interval (CI) set to 95%. A value of $P < .05$ was considered to be statistically significant.

2.6. Ethical statement

As this meta-analysis was based on previously published studies ethical approval was not necessary.

3. Results

3.1. Characteristics of included studies

Initially, 1109 potentially relevant articles were screened using relevant words. Among them 850 were excluded. After the full-text review of the studies, 240 studies were excluded due to exclusion criteria. Finally, 19 eligible studies are included. Figure 1 shows the selection process of published trials for this systematic review. A total of 19 RCTs involving 6812 patients were ultimately included in this analysis (placebo, ANA, ABA, ETN, MTX, placebo + MTX, ANA + MTX, ETN + MTX, ETN + placebo, MTX + placebo). All studies meet the inclusion criteria of the literature and show the basic characteristics of the studies are summarized in Table 1.

3.2. Network meta-analysis
3.2.1. Network plot of 8 different fusion proteins combinations.
Of the 19 publications involving 6812 patients, studies on the combination of placebo + MTX were the most frequent, while those on ANA and ABA alone were the least frequent. The placebo + MTX group had the highest number of subjects, while ABA had the lowest number of subjects (Fig. 2).

3.2.2. Evidence contribution plot.
The direct comparison of ETN alone and the combination of ETN + MTX had a 99% effect on the combined result. The direct comparison between ETN alone and ETN + MTX had a 25% effect on the indirect comparison between ANA and ABA. The direct comparison of
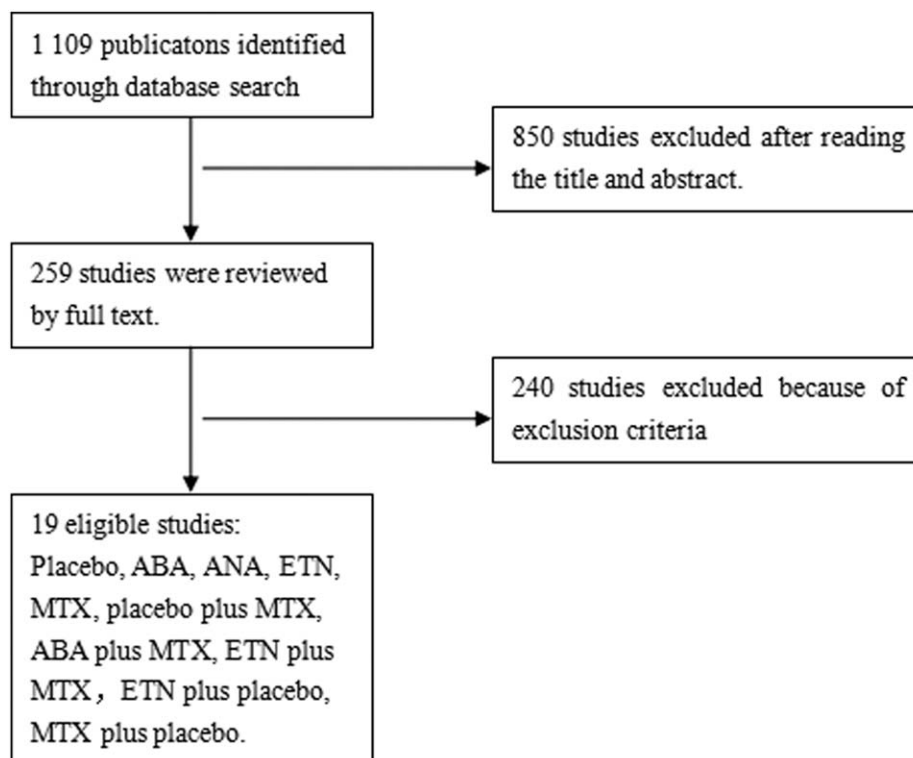
Figure 1. Flow diagram of the selected details of included publications.

| Table 1 |

Basic information of included studies in the network meta-analysis.

Study	Country	Cases	Control	Cases	Total cases	Control	Total Control	Duration of follow-up (mouth)	Jadad quality score
Nuki et al (2002)[16]	Europe	C	A	84	233	11	76	6	4
Cohen (2004)[17]	USA	F	J	95	250	55	251	6	3
Cohen et al (2002)[18]	Canada, Australia, USA	F	J	68	269	7	48	6	4
Emery et al (2015)[19]	USA, Europe	D	J	50	116	53	116	12	4
		G		73	119				
Westhovens et al (2014)[20]	Belgium	G	J	100	152	19	67	12	4
Takeuchi et al (2013)[21]	Japan	G	J	89	128	14	66	6	4
Matsubara et al (2018)[22]	Japan	G	J	153	203	56	202	4	4
Schiff et al (2008)[23]	USA	G	J	104	156	46	110	6	4
Kremer et al (2006)[24]	USA	G	J	294	433	87	219	12	4
Kremer et al (2005)[25]	USA	G	J	72	115	43	119	12	4
Weinblatt et al (2007)[26]	USA	G	I	41	85	11	36	12	4
van Riel et al (2006)[27]	Denmark, Finland, France, etc	E	H	110	155	102	152	4	3
Kameda et al (2010)[28]	Japan	E	H	44	69	66	73	6	4
Keystone et al (2004)[29]	USA, Canada	E	A	182	367	10	53	2	4
Bassiouni et al (2018)[30]	African, Middle Eastern	E	A	18	22	20	29	6	3
van der Heijde et al (2006)[31]	The Netherlands	E	B	167	223	162	228	24	4
		H		199	231				
Takeuchi et al (2013)[32]	Japan	H	B	288	373	110	176	12	4
Smolen et al (2013)[33]	Europe, Latin America, Asia, etc	H	I	301	401	96	197	24	4
Gallo et al (2016)[34]	Italy	H	B	254	276	168	218	20	3

A = placebo, B = MTX, C = ANA, D = ABA, E = ETN, F = ANA + MTX, G = ABA + MTX, H = ETN + MTX, I = ETN + placebo, J = MTX + placebo.
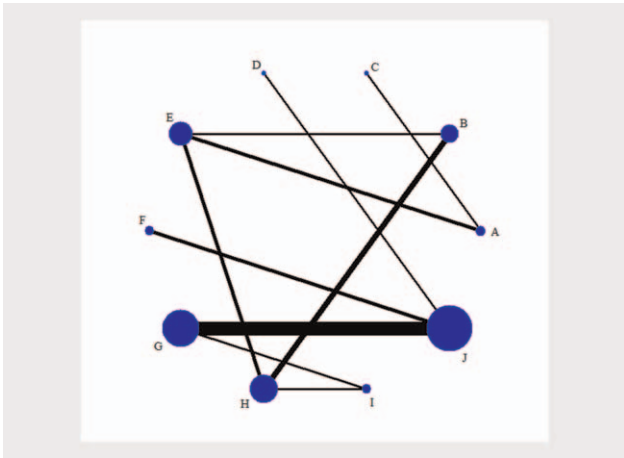
Figure 2. Network plot of different interventions for the treatment of RA. The size of the point in the network graph is proportional to the number of subjects, while the thickness of the line is proportional to the number of studies. A=placebo, B=MTX, C=ANA, D=ABA, E=ETN, F=ANA+MTX, G=ABA+MTX, H=ETN+MTX, I=ETN+placebo, J=MTX+placebo. ABA=abatacept, ANA=anakinra, ETN=etanercept, MTX=methotrexate.

ETN alone and ETN+MTX had a 6.8% effect on the results of the meta-analysis (Fig. 3).

3.2.3. Predictive interval plot. It is showed that the pooled OR and 95% CI of RA improvement compared with placebo alone were 2.44(0.75, 7.92) for MTX, 3.33(1.06, 10.45) for ANA, 0.93 (0.10, 8.79) for ABA, 3.30(1.28, 8.47) for ETN, 2.17(0.28, 18.33) for ANA+MTX, 4.05(0.58, 28.41) for ABA+MTX, 6.06 (1.92, 19.18) for ETN+MTX, 1.91(0.42, 8.67) for ETN+ placebo, and 1.03(0.14, 7.54) for MTX+placebo, respectively. The OR for the network estimates along with 95% CI and PrI is presented in Figure 4.

3.2.4. Publication bias. Regarding publication bias, all the outcomes in the study were not exactly symmetrical (Fig. 5), suggesting that the publication bias may have existed.

3.2.5. Ranking plot. The distribution of probabilities for each treatment being ranked for their efficacy in RA according to SUCRA values is presented in Table 2 and Figure 6. The order of SUCRA values for different aspirin combinations was as follows: ETN+MTX (91.6), ABA+MTX (76.6), ETN (67.1), ANA (64.9), MTX (51.8), ANA+MTX (50.1), ETN+placebo (42.2), MTX+placebo (19.1), ABA (18.5), and placebo (18.2).

Figure 3. Evidence contribution plot. The matrix showed the effect of comparing the results of different control measures directly with the results of their network meta-analysis. A=placebo, B=MTX, C=ANA, D=ABA, E=ETN, F=ANA+MTX, G=ABA+MTX, H=ETN+MTX, I=ETN+placebo, J=MTX+placebo. ABA= abatacept, ANA=anakinra, ETN=etanercept, MTX=methotrexate.

Figure 4. Network estimates of mean *OR*, their 95% CIs and prediction intervals (red extensions). A=placebo, B=MTX, C=ANA, D=ABA, E=ETN, F=ANA+MTX, G=ABA+MTX, H=ETN+MTX, I=ETN+placebo, J=MTX+placebo. ABA=abatacept, ANA=anakinra, ETN=etanercept, MTX=methotrexate.
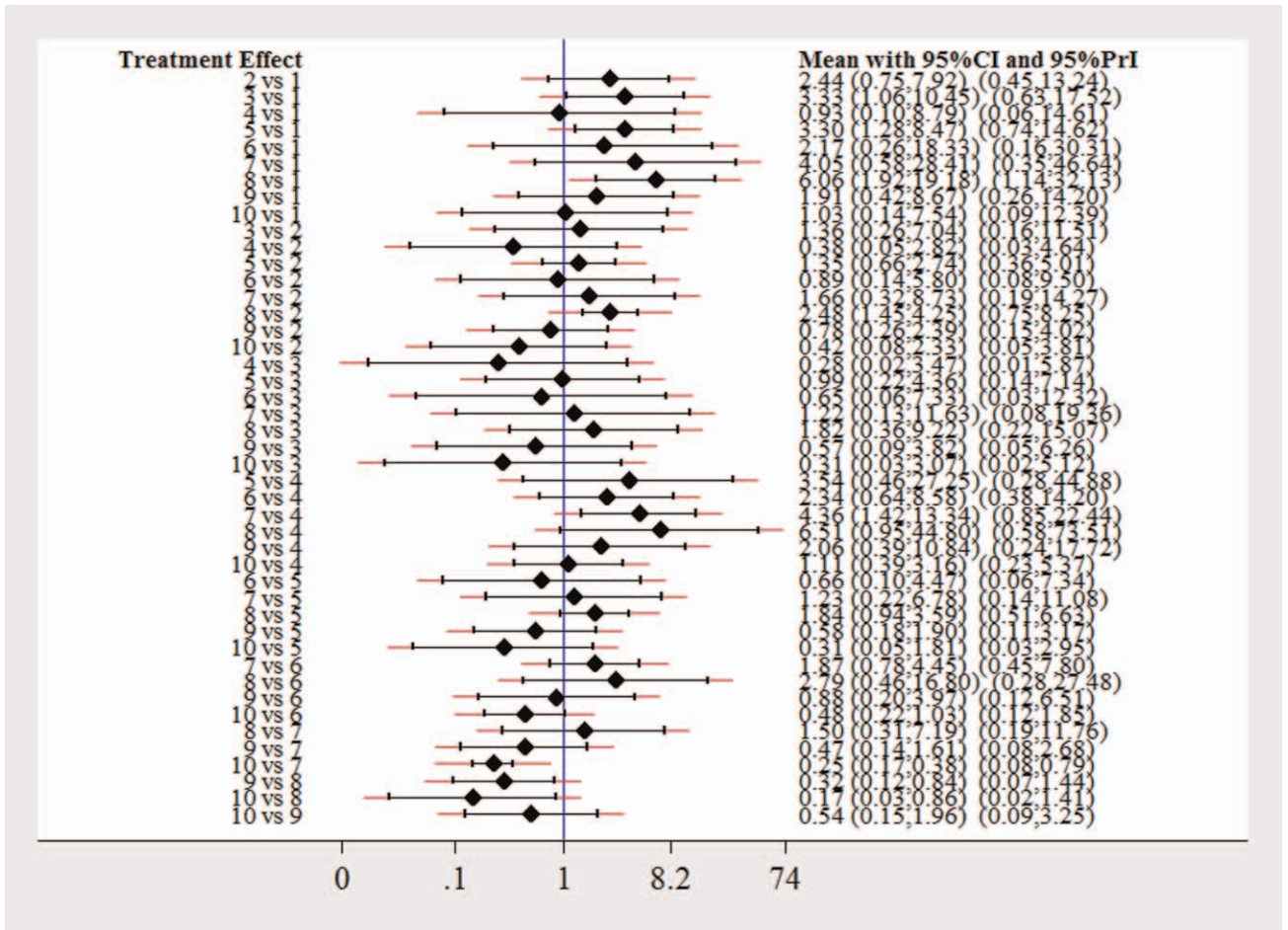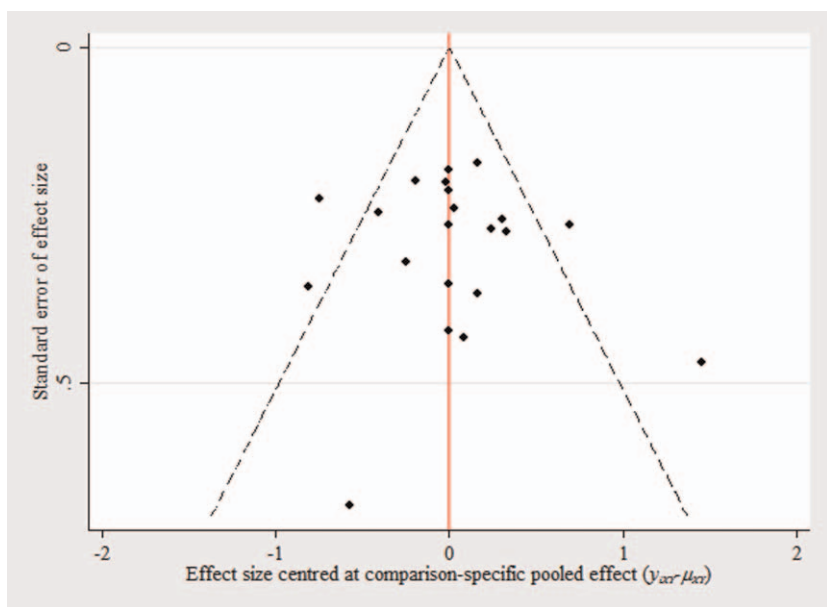

Figure 5. Funnel plot for publication bias in selected studies.

Table 2

SUCRA of acute cerebral infarction treatments.

Treatment	SUCRA	Pr best	Mean
A	18.5	0.0	8.3
B	51.8	0.0	5.3
C	64.9	19.5	4.2
D	18.2	0.1	8.4
E	67.1	1.4	4.0
F	50.1	2.8	5.5
G	76.6	24.5	3.1
H	91.6	51.6	1.8
I	42.2	0.1	6.2
J	19.1	0.0	8.3

A = placebo, B = MTX, C = ANA, D = ABA, E = ETN, F = ANA + MTX, G = ABA + MTX, H = ETN + MTX, I = ETN + placebo, J = MTX + placebo.

Therefore, the combination of ETN with MTX had the highest probability of being the best intervention option in terms of clinical efficacy.

4. Discussion

This study analyzed 10 different combinations, which consisting of 3 fusion proteins or placebo or MTX. The resulting network

shows that the combination of ETN with MTX had the highest probability of being the best treatment option of 8 combinations, and the SUCRA value was 91.6. ENT, ENT + MTX, and ANA were effective in the treatment of RA compared to placebo.

RA is 1 of the chronic inflammatory autoimmune diseases, leading to the function of other organs and tissues are damaged including symmetrical joints. Although the pathogenesis of RA still obscures, Matsuno et al[35] has provided that tumor necrosis factor (TNF) is a key molecule that controls the inflammatory changes that occur in the RA synovium. In recent years, people have found biologics have been essential for increasing the likelihood of disease remission and low disease activity.[36] Fusion protein is 1 of the biological agents, product a novel single protein with 2 partial functional properties, produced by genetic fusion of 2 or more genes.[37] One part of the structure of the fusion protein provides molecular binding while the other part has certain functions.[38] The functions part is called fc, which binding to specific receptors to achieve pharmaceutic properties of the construct.[39] ETN is 1 of the fusion proteins that was first applied to the clinical treatment of RA.[40] The pathogenesis of RA was classically viewed as the deregulation of Th1/Th2 balance, and that these cells secrete pro-inflammatory cytokines with a subset of TNF-pcr T helper cells.[41] Recently, we have known that CD4 + CD25 high regulatory T cells (Treg cells) and
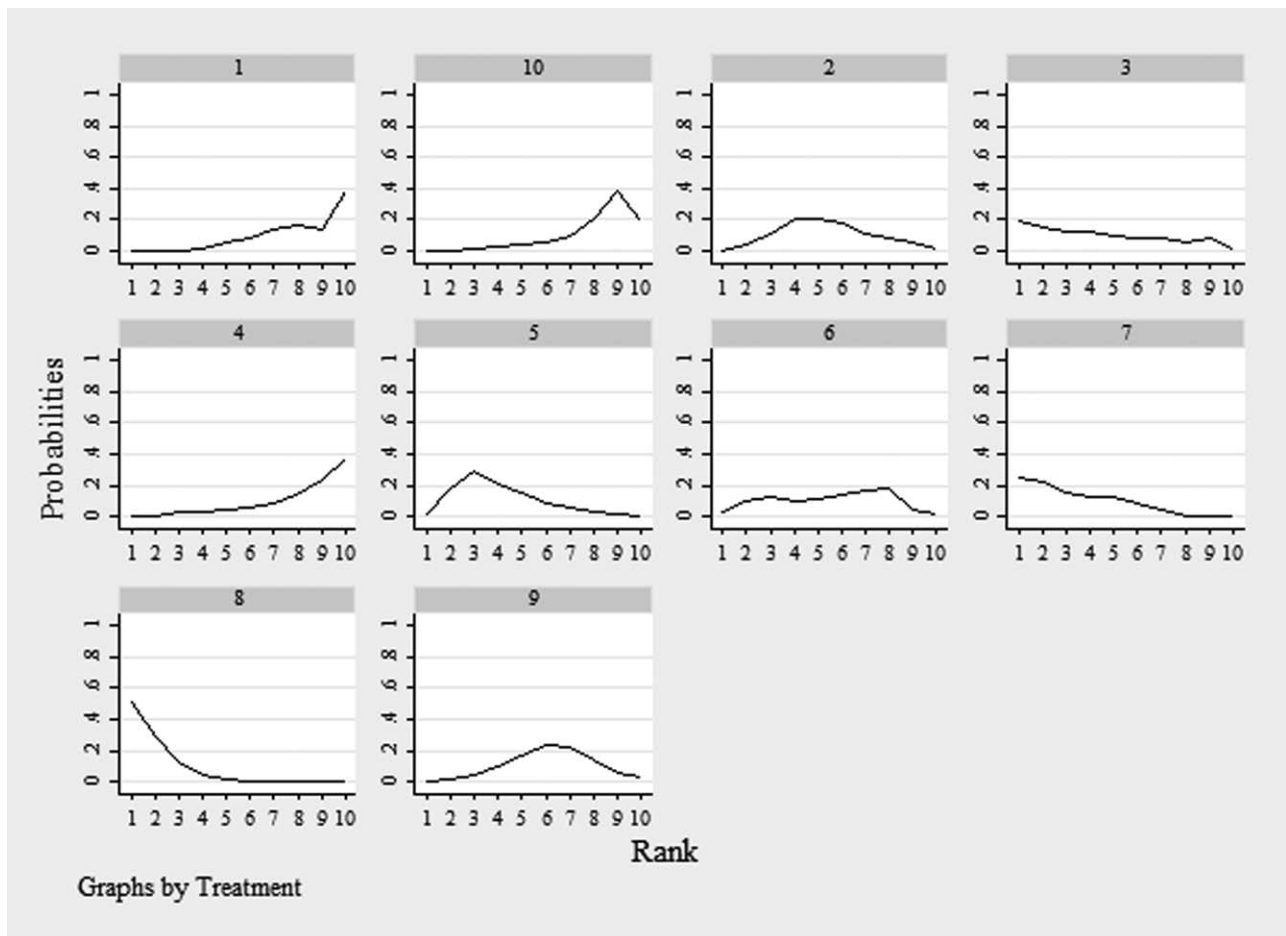
Figure 6. SUCRA for the cumulative probabilities. A = placebo, B = MTX, C = ANA, D = ABA, E = ETN, F = ANA + MTX, G = ABA + MTX, H = ETN + MTX, I = ETN + placebo, J = MTX + placebo. ABA = abatacept, ANA = anakinra, ETN = etanercept, MTX = methotrexate, SUCRA = surface values under the cumulative ranking.

newly reported IL-17-producing Th17 cells may challenge this classical theory. Therefore, the balance between Th17 and Treg, as well as Th1/Th2, has long been considered as 1 of the important factors in the treatment of autoimmune diseases including RA.[42] Anti-TNF therapy may lead to the failure of the Treg suppression effect on cell proliferation to reduce Foxp3 mRNA expression.[43] ETN, as a kind of TNF-α inhibitors, is the first TNF-α inhibitor for the treatment of RA. ETN can affect the production of various cytokines, chemokines, and proteases, possibly downstream of a pot of TNF-α cascade and regulating inflammatory processes in RA.[44] Lina et al[42] found that the combination of ETN and MTX can ameliorate the activity of the disease by regulating the differentiation or function of Th17 and Treg, and the patients treated with MTX alone showed no significant reversal of Th1/Th2 or Th17/Treg imbalances and no satisfactory remission after 12 weeks of treatment. Patients taking the combination of ETN and MTX reduced plasma interleukin-1 (IL-1) exposure, TNF-α, IL-6, IL-17, IL-23, and increased TGF-β. ANA is an IL-1 receptor antagonist (IL-1ra), which blocks IL-1, involved in inflammation; a protein associated with joint destruction for RA.[45] ABA was composed of the extracellular domain and Fc portion of cytotoxic T lymphocyte-associated protein 4 (CTLA-4), which works by binding to the differential (CD)80/86 cluster on antigen-presenting cells (APC) and blocking the B7:CD28 interaction, then inhibiting joint inflammation.[46]

In this study, the combination of MTX and ETN agents had the highest probability of optimal treatment compared to other drugs. Iannone et al[47] reached a similar conclusion that the combination of MTX and biologic agents more effective than MTX alone, which consistent with this study. The combination of ETN with MTX had the highest probability of being the best intervention option in terms of clinical efficacy. ENT, ENT+ MTX, and ANA were effective in the treatment of RA compared to placebo. However, the adverse effects of biological agents have always been the focus of attention, and how to customize individualized biological therapies has always been valued by people. The combined use of drugs needs to consider the tolerance of RA patients. Inconsistencies may have an impact on the arguments raised by the use of only ACR20 criteria to evaluate the efficacy and quality of the original publication used. The results may be affected by inconsistent literature quality, the heterogeneity inherent in RA, and different ethnicities and sample sizes. Future research involving high-quality RCTs and large sample sizes is needed.

5. Conclusions

The combination of ETN and MTX had the highest probability of optimal treatment compared to other drugs; ENT, ENT+ MTX, and ANA were effective in the treatment of RA compared to placebo.

Acknowledgments

Author contributions

Conceptualization: Mingcai Wu.

Data curation: Quanhai Wang, Hui Yuan.
Formal analysis: Quanhai Wang.
Methodology: Xiaohua Lu.
Project administration: Mingcai Wu, Mengjun Tao.
Software: Mingcai Wu, Mengjun Tao.
Supervision: Hui Yuan.
Writing – original draft: Mingcai Wu, Mengjun Tao.
Writing – review & editing: Mingcai Wu, Mengjun Tao.

References

[1] Barhamain AS, Magliah RF, Shaheen MH, et al. The journey of rheumatoid arthritis patients: a review of reported lag times from the onset of symptoms. Open Access Rheumatol 2017;28:139–50.

[2] Hillen J, Geyer C, Heitzmann M, et al. A structural cartilage damage attracts circulating rheumatoid arthritis synovial fibroblasts into affected joints. Arthritis Res Ther 2017;19:4028.

[3] Abushouk AI, Ahmed H, Ismail A, et al. Safety and efficacy of ocrelizumab in rheumatoid arthritis patients with an inadequate response to methotrexate or tumor necrosis factor inhibitors: a systematic review and meta-analysis. Rheumatol Int 2017;37:1053–64.

[4] Rifbjerg-Madsen S, Christensen AW, Christensen R, et al. Pain and pain mechanisms in patients with inflammatory arthritis: a Danish nationwide cross-sectional DANBIO registry survey. PLoS One 2017;12:e0180014.

[5] Zhang L, Wang J, Zhang Q, et al. Factors associated with hand joint destruction in Chinese patients with rheumatoid arthritis. BMC Musculoskelet Disord 2017;18:211.

[6] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 2017;389:2328–37.

[7] Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. Pharmacoeconomics 2014;32:841–51.

[8] Takeda T. Treatment strategy of elderly rheumatoid arthritis. Nihon Rinsho Meneki Gakkai Kaishi 2016;39:497–504.

[9] Hyndman IJ. Rheumatoid arthritis: past, present and future approaches to treating the disease. Int J Rheum Dis 2017;20:417–9.

[10] Kaneko Y, Takeuchi T. Targeted antibody therapy and relevant novel biomarkers for precision medicine for rheumatoid arthritis. Int Immunol 2017;29:511–7. 30.

[11] Chen X, Zhao Q, Hou Y, et al. Pharmacokinetics, pharmacodynamics, short term efficacy and safety of RCT-18, a novel BLyS/APRIL fusion protein, in patients with rheumatoid arthritis. Br J Clin Pharmacol 2016;82:41–52.

[12] Tao MJ, Cheng P, Jin LR, et al. The safety and efficacy of biologic agents in treatment of systemic lupus erythematosus: a network meta-analysis. Pak J Med Sci 2019;35:1680–6.

[13] Ghafar MTA, Haleem SA, Shahba A, Sweilam AM. Diagnostic value of the serum Midkine in patients with rheumatoid arthritis. J Investig Med 2019;68: jim-2019-001097.

[14] Aletaha D, Neoji T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

[15] Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609–13.

[16] Nuki G, Bresnihan B, Bear MB, McCabe D. European Group of Clinical Investigators.Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:2838–46.

[17] Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis 2004;63:1062–8.

[18] Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multi-center, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614–24.

[19] Emery P, Burmester GR, Bykerk VP, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b,

multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19–26.

[20] Westhovens R, Kremer JM, Emery P, et al. Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. Clin Exp Rheumatol 2014;32:553–62.

[21] Takeuchi T, Matsubara T, Nitobe T, et al. Phase II dose–response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol 2013;23:226–35.

[22] Matsubara T, Inoue H, Nakajima T, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. RMD Open 2018;4:e000813.

[23] Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096–103.

[24] Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.

[25] Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:2263–71.

[26] Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis 2007;66:228–34.

[27] van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006;65:1478–83.

[28] Kameda H, Ueki Y, Saito K, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol 2010;20:531–8.

[29] Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50:353–63.

[30] Bassiouni H, Spargo CE, Vlahos B, Jones HE, Pedersen R, Shirazy K. Maintenance of remission with etanercept-DMARD combination therapy compared with DMARDs alone in African and Middle Eastern patients with active rheumatoid arthritis. Rheumatol Ther 2018;5:149–58.

[31] van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063–74.

[32] Takeuchi T, Miyasaka N, Zang C, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol 2013;23:623–33.

[33] Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013;381:918–29.

[34] Gallo G, Brock F, Kerkmann U, Kola B, Huizinga TW. Efficacy of etanercept in combination with methotrexate in moderate-to-severe rheumatoid arthritis is not dependent on methotrexate dosage. RMD Open 2016;2:e000186.

[35] Matsuno H, Yudoh K, Katayama R, et al. The role of TNF-alpha in the pathogenesis of inflammation and joint destruction in rheumatoid arthritis (RA): a study using a human RA/SCID mouse chimera. Rheumatology (Oxford) 2002;41:329–37.

[36] Tanaka Y. Current concepts in the management of rheumatoid arthritis. Korean J Intern Med 2016;31:210–8.

[37] Chen X, Zaro JL, Shen WC. Pharmacokinetics of recombinant bifunctional fusion proteins. Expert Opin Drug Metab Toxicol 2012;8:581–95.

[38] Shamriz S, Ofoghi H, Moazami N. Effect of linker length and residues on the structure and stability of a fusion protein with malaria vaccine application. Comput Biol Med 2016;76:24–9.

[39] Lee S, Ballow M. Monoclonal antibodies and fusion proteins and their complications: targeting B cells in autoimmune diseases. J Allergy Clin Immunol 2010;125:814–20.

[40] Cañete JD, Hernández MV, Sanmartí R. Safety profile of biological therapies for treating rheumatoid arthritis. Expert Opin Biol Ther 2017;17:1089–103.

[41] McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007;7:429–42.

[42] Lina C, Conghua W, Nan L, Ping Z. Combined treatment of etanercept and MTX reverses Th1/Th2, Th17/Treg imbalance in patients with rheumatoid arthritis. J Clin Immunol 2011;31:596–605.

[43] Carmona L, Gomez-Reino JJ. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Arthritis Res Ther 2006;8:R72.

[44] Kageyama Y, Ichikawa T, Nagafusa T, Torikai E, Shimazu M, Nagano A. Etanercept reduces the serum levels of interleukin-23 and macrophage inflammatory protein-3 alpha in patients with rheumatoid arthritis. Rheumatol Int 2007;28:137–43.

[45] Garces K. Anakinra: interleukin-1 receptor antagonist therapy for rheumatoid arthritis. Issues Emerg Health Technol 2001;16:1–4.

[46] Oryoji K, Yoshida K, Kashiwado Y, et al. Shared epitope positivity is related to efficacy of abatacept in rheumatoid arthritis. Ann Rheum Dis 2018;77:1234–6.

[47] Iannone F, Lopalco G, Cantarini L, Galeazzi FM, Lapadula G. Efficacy and safety of combination therapy for preventing bone damage in rheumatoid arthritis. Clin Rheumatol 2016;35:19–23.