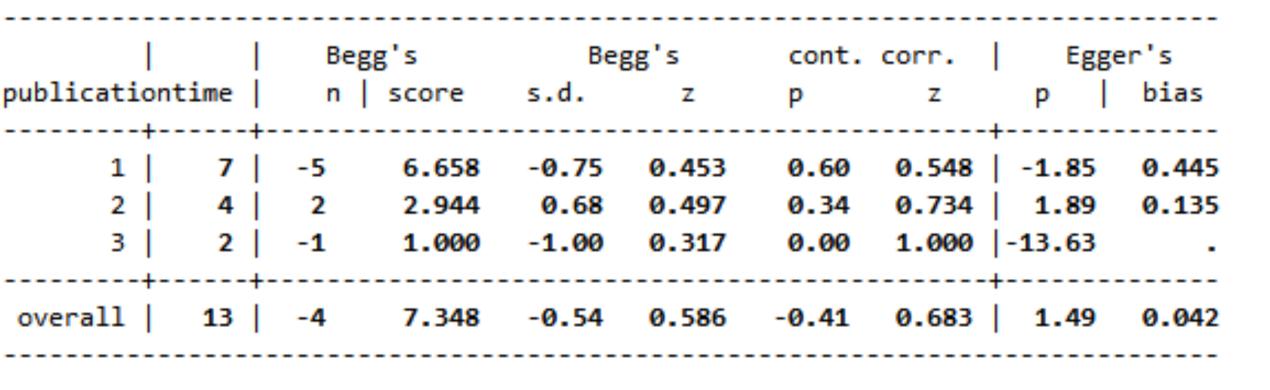
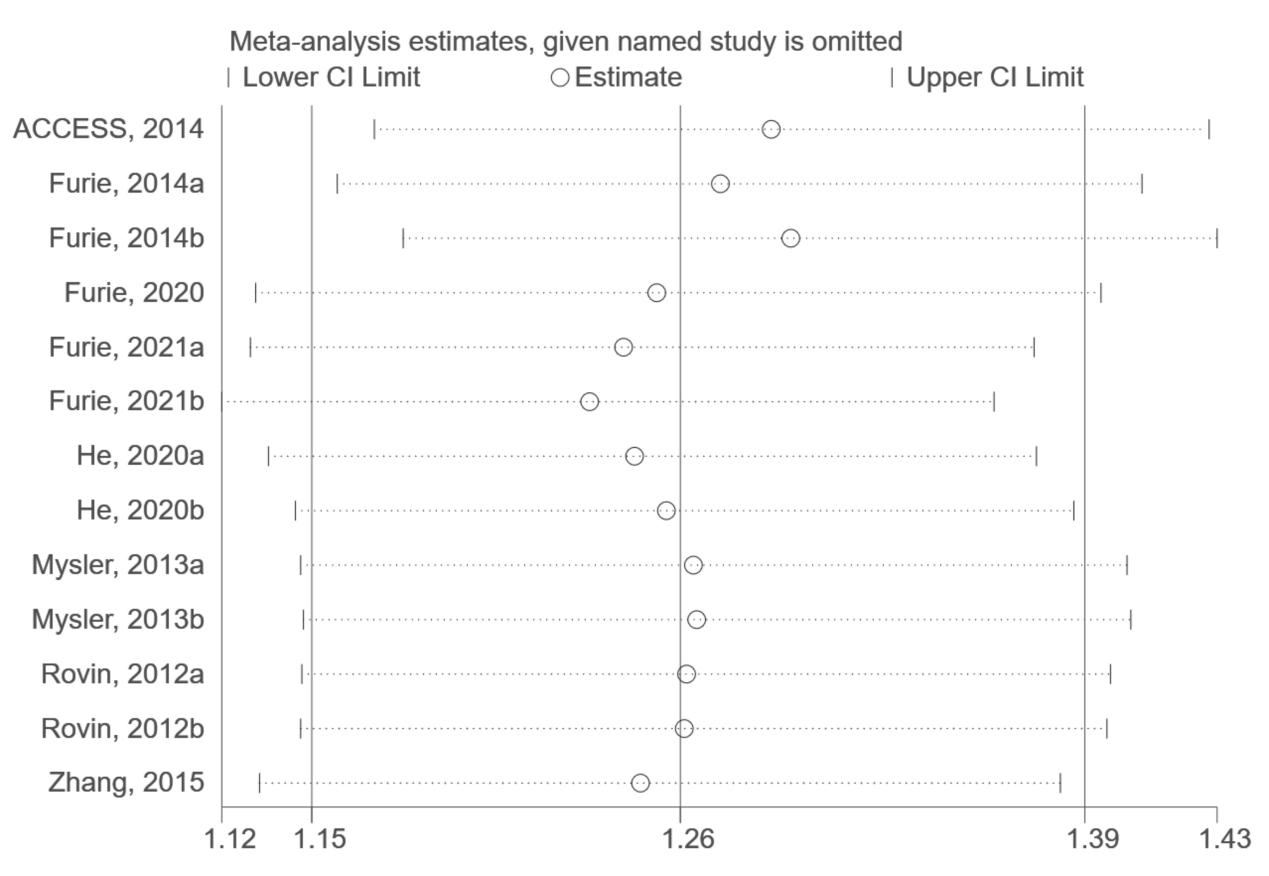


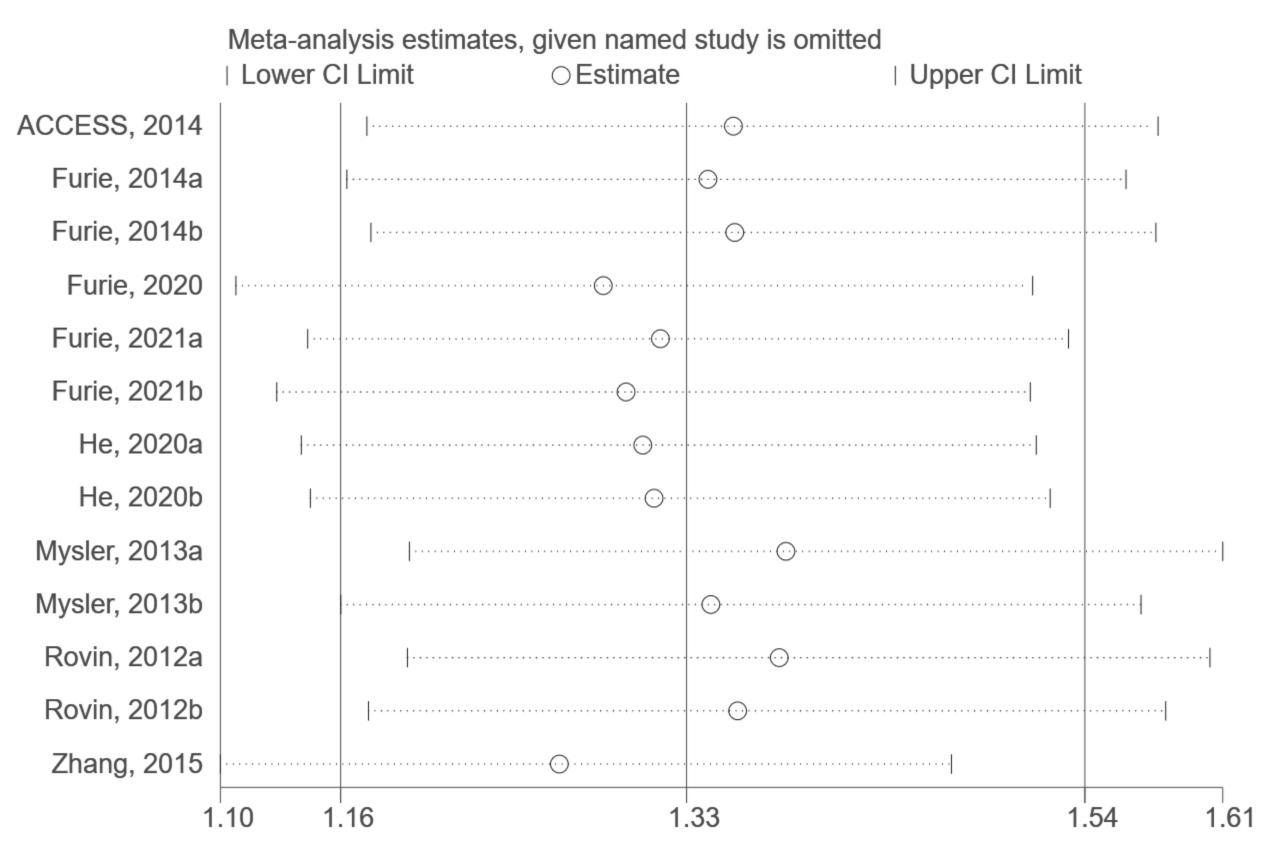
**Supplementary Figure S1.** Forest plot of complete response by publication time. 1: Published from 2012 to 2014. 2: Published from 2015 to 2020. 3: Published in 2021. 4: Overall.



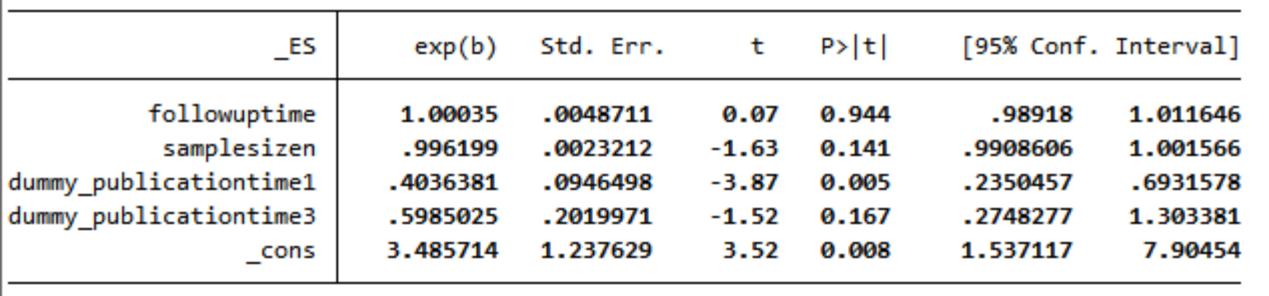
**Supplementary Figure S2.** Publication bias of complete response by publication time.



**Supplementary Figure S3.** Sensitivity analysis of overall response.



**Supplementary Figure S4.** Sensitivity analysis of complete response.



**Supplementary Figure S5.** Meta-regression of complete response.

**Supplementary Table S1.** Search strategy

|  |  |  |  |
| --- | --- | --- | --- |
| **PubMed** |  | **Search strategy** | **Numbers** |
| **Patient** | **#1** | "Lupus Nephritis"[Mesh] | 7078 |
|  | **#2** | ((((((Lupus Glomerulonephritis[Title/Abstract]) OR (Nephritis, Lupus[Title/Abstract])) OR (Lupus Nephritides[Title/Abstract])) OR (Nephritides, Lupus[Title/Abstract])) OR (Glomerulonephritis, Lupus[Title/Abstract])) OR (Glomerulonephritides, Lupus[Title/Abstract])) OR (Lupus Glomerulonephritides[Title/Abstract]) | 12,754 |
|  | **#3** | **#1** OR **#2** | 13,234 |
| **Intervention** | **#4** | "Biological Factors"[Mesh] | 3,455,749 |
|  | **#5** | ((((((((((((((Biological Agent[Title/Abstract]) OR (Agent, Biological[Title/Abstract])) OR (Biological Factor[Title/Abstract])) OR (Biologic Agents[Title/Abstract])) OR (Agents, Biologic[Title/Abstract])) OR (Factors, Biological[Title/Abstract])) OR (Biologic Factors[Title/Abstract])) OR (Factors, Biologic[Title/Abstract])) OR (Factor, Biologic[Title/Abstract])) OR (Biologic Factor[Title/Abstract])) OR (Biological Agents[Title/Abstract])) OR (Agents, Biological[Title/Abstract])) OR (Biologic Agent[Title/Abstract])) OR (Agent, Biologic[Title/Abstract])) OR (Factor, Biological[Title/Abstract]) | 12,097 |
|  | **#6** | **#4** OR **#5** | 3,464,439 |
|  | **#7** | (((((((((((((((((Belimumab[Title/Abstract]) OR (Tabalumab[Title/Abstract])) OR (Blisibimod[Title/Abstract])) OR (Atacicept[Title/Abstract])) OR (Rituximab[Title/Abstract])) OR (Ocrelizumab[Title/Abstract])) OR (Epratuzumab[Title/Abstract])) OR (Bortezomib[Title/Abstract])) OR (Abatacept[Title/Abstract])) OR (P140[Title/Abstract])) OR (lupuzor[Title/Abstract])) OR (Edratide[Title/Abstract])) OR (pConsensus[Title/Abstract])) OR (Sifalimumab[Title/Abstract])) OR (Rontalizumab[Title/Abstract])) OR (Anifrolumab[Title/Abstract])) OR (AMG811[Title/Abstract])) OR (Toculizumab[Title/Abstract]) | 34,630 |
|  | **#8** | **#6** AND **#7** | 3,491,192 |
| **Outcome** | **#9** | ((((((((((complete remission) OR (complete response)) OR (total remission)) OR (overall response)) OR (total response)) OR (overall remission)) OR (partial remission)) OR (partial response)) OR (urinary protein)) OR (renal activity index)) OR (AI) | 4,154,938 |
| **P+I+O** | **#10** | **#3** AND **#8** AND **#9** | 2680 |
| **Study type** | **#11** | (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])) | 1,306,134 |
| **P+I+O+S** | **#12** | #10 AND #11 | 132 |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| Embase |  | Search strategy | Numbers |
| Patient | **#1** | 'lupus erythematosus nephritis'/exp | 18,540 |
|  | **#2** | 'glomerulonephritis, lupoid':ab,ti OR 'lupoid nephritis':ab,ti OR 'lupus erythematosus, nephritis':ab,ti OR 'lupus glomerulonephritis':ab,ti OR 'lupus kidney':ab,ti OR 'lupus nephritis':ab,ti OR 'lupus nephropathy':ab,ti OR 'nephritis, lupus erythematosus':ab,ti OR 'nephritis, systemic lupus erythematosus':ab,ti OR 'systemic lupus erythematosis, nephritis':ab,ti | 15,359 |
|  | **#3** | **#1** OR **#2** | 20,419 |
| Intervention | **#4** | 'biological product'/exp | 807,796 |
|  | **#5** | 'biologic agent':ab,ti OR 'biologic agents':ab,ti OR 'biologic product':ab,ti OR 'biologic products':ab,ti OR 'biological agent':ab,ti OR 'biological agents':ab,ti OR 'biological products':ab,ti | 19,455 |
|  | **#6** | **#4** OR **#5** | 820,316 |
|  | **#7** | 'Belimumab':ab,ti OR 'Tabalumab':ab,ti OR 'Blisibimod':ab,ti OR 'Atacicept':ab,ti OR 'Rituximab':ab,ti OR 'Ocrelizumab':ab,ti OR 'Epratuzumab':ab,ti OR 'Bortezomib':ab,ti OR 'Abatacept':ab,ti OR 'P140':ab,ti OR 'lupuzor':ab,ti OR 'Edratide':ab,ti OR 'pConsensus':ab,ti OR 'Sifalimumab':ab,ti OR 'Rontalizumab':ab,ti OR 'Anifrolumab':ab,ti OR 'AMG811':ab,ti OR 'Toculizumab':ab,ti | 77,306 |
|  | **#8** | **#6** OR **#7** | 893,217 |
| Outcome | **#9** | 'complete remission':ab,ti OR 'complete response':ab,ti OR 'total remission':ab,ti OR 'overall response':ab,ti OR 'total response':ab,ti OR 'overall remission':ab,ti OR 'partial remission':ab,ti OR 'partial response':ab,ti OR 'urinary protein':ab,ti OR 'renal activity index':ab,ti OR 'AI':ab,ti | 245,293 |
| P+I+O | **#10** | **#3** AND **#8** AND **#9** | 206 |
| Study type | **#11** | 'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR 'randomi?ed controlled' NEXT/1 trial\* OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR allocated NEAR/2 random OR single NEXT/1 blind\* OR double NEXT/1 blind\* OR (treble OR triple) NEAR/1 blind\* OR placebo\* | 2,589,380 |
| P+I+O+S | **#12** | **#10** AND **#11** | 87 |

|  |  |  |  |
| --- | --- | --- | --- |
| Cochrane |  | Search strategy | Numbers |
| Patient | **#1** | MeSH descriptor: [Lupus Nephritis] explode all trees | 261 |
|  | **#2** | (Lupus Glomerulonephritis):ti,ab,kw OR (Nephritis, Lupus):ti,ab,kw OR (Lupus Nephritides):ti,ab,kw OR (Nephritides, Lupus):ti,ab,kw OR (Glomerulonephritis, Lupus):ti,ab,kw OR (Glomerulonephritides, Lupus):ti,ab,kw OR (Lupus Glomerulonephritides):ti,ab,kw | 937 |
|  | **#3** | **#1** OR **#2** | 937 |
| Intervention | **#4** | MeSH descriptor: [Biological Factors] explode all trees | 77,906 |
|  | **#5** | (Biological Agent):ti,ab,kw OR (Agent, Biological):ti,ab,kw OR (Biological Factor):ti,ab,kw OR (Biologic Agents):ti,ab,kw OR (Agents, Biologic):ti,ab,kw OR (Factors, Biological):ti,ab,kw OR (Biologic Factors):ti,ab,kw OR (Factors, Biologic):ti,ab,kw OR (Factor, Biologic):ti,ab,kw OR (Biologic Factor):ti,ab,kw OR (Biological Agents):ti,ab,kw OR (Agents, Biological):ti,ab,kw OR (Biologic Agent):ti,ab,kw OR (Agent, Biologic):ti,ab,kw OR (Factor, Biological):ti,ab,kw | 14,199 |
|  | **#6** | **#4** OR **#5** | 89,923 |
|  | **#7** | (Belimumab):ti,ab,kw OR (Tabalumab):ti,ab,kw OR (Blisibimod):ti,ab,kw OR (Atacicept):ti,ab,kw OR (Rituximab):ti,ab,kw OR (Ocrelizumab):ti,ab,kw OR (Epratuzumab):ti,ab,kw OR (Bortezomib):ti,ab,kw OR (Abatacept):ti,ab,kw OR (P140):ti,ab,kw OR (lupuzor):ti,ab,kw OR (Edratide):ti,ab,kw OR (pConsensus):ti,ab,kw OR (Sifalimumab):ti,ab,kw OR (Rontalizumab):ti,ab,kw OR (Anifrolumab):ti,ab,kw OR (AMG811):ti,ab,kw OR (Toculizumab):ti,ab,kw | 8722 |
|  | **#8** | **#6** OR **#7** | 97,955 |
| P+I | **#9** | **#3** AND **#8** | 181 |
| Outcome | **#10** | (complete remission) OR (complete response) OR (total remission) OR (overall response) OR (total response)OR (overall remission) OR (partial remission) OR (partial response) OR (urinary protein) OR (renal activity index) OR (AI) | 129,494 |
| P+I+O | **#11** | #9 AND #10 | 91 (1R+90T) |

**Supplementary Table S2. Characteristics of the included studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Country** | **Sample size (n)** | **Intervention** | **Control** | **Age (M/sd)** | **Follow-up times** | **Participants** | **Outcome** |
| ACCESS, 2014 (18) | USA,  Mexico | 66/68 | Abatacept | Placebo | 32.0±10.1/ 32.7±12.0 | 24 weeks | Active lupus nephritis | Overall response, complete response, AEs, UPr:Cr |
| Furie, 2014 (19) | North America, Europe, South America, Asia, Australia, India, South Africa, and Turkey | 99/99/100 | Abatacept | Placebo | 31.0±9.5/ 30.5±10.6/ 31.8±9.0 | 52 weeks | Active class III or IV glomerulonephritis (with or without class V) | Overall response, complete response, AEs |
| Furie, 2020 (13) | 21 countries | 224/224 | Belimumab | Placebo | 33.7±10.7/ 33.1±10.6 | 104 weeks | Biopsy proven lupus nephritis | Overall response, complete response, AEs |
| Furie, 2021 (20) | North America, South America, Europe and Israel | 63/62 | Obinutuzumab | Placebo | 33.1±9.8/ 31.9±10.1 | a.52 weeks; b.104 weeks | Class III or IV active or active/chronic LN within 6 months of screening | Overall response, complete response, AEs |
| Ginzler, 2012 (21) | USA | 4/2 | Atacicept | Placebo | / | 14 days | Active LN (class III or IV LN) | UPr:Cr |
| He, 2020 (22) | China | 13/12 | IL-2 | Placebo | / | a.12 weeks; b.24 weeks | SLE patients | Overall response, complete response |
| Mysler, 2013 (23) | USA | 128/127/126 | Ocrelizumab | Placebo | 30.6 (16–60)/ 31.9 (16–69)/ 31.3 (17–66) | 48 weeks | SLE, including a history of antinuclear antibody positivity and active LN | Overall response, complete response, AEs |
| Rovin, 2012 (12) | USA | 72/72 | Rituximab | Placebo | 31.8 ± 9.6/ 29.4 ± 9.3 | a.52 weeks; b.78 weeks | SLE was required to have a history of antinuclear antibody positivity, class III or class IV (± class V) LN | Overall response, complete response, AEs |
| Zhang, 2015 (24) | China | 42/42 | Rituximab | Placebo | / | 12 months | Refractory severe LN | Overall response, complete remission |

ACCESS: the Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study; AEs: adverse events; UPr:Cr: Urinary protein-to-creatinine ratio; LN: lupus nephritis; SLE: systemic lupus erythematosus.

**Supplementary Table S3. Cochrane criteria for the quality of RCTs**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Random sequence generation (selection bias)** | **Allocation concealment (selection bias)** | **Blinding of participants and personnel (performance bias)** | **Blinding of outcome assessment (detection bias)** | **Incomplete outcome data (attrition bias)** | **Selective reporting (reporting bias)** | **Other bias** | **Total quality scores** |
| ACCESS, 2014 (18) |  | \* | \* | \* | \* | \* | \* | 6 |
| Furie, 2014 (19) |  | \* | \* | \* | \* | \* | \* | 6 |
| Furie, 2020 (13) | \* | \* | \* | \* | \* | \* | \* | 7 |
| Furie, 2021 (20) | \* | \* | \* | \* | \* | \* | \* | 7 |
| Ginzler, 2012 (21) |  | \* | \* | \* | \* | \* | \* | 6 |
| He, 2020 (22) |  | \* | \* | \* | \* | \* | \* | 6 |
| Mysler, 2013 (23) |  | \* | \* | \* | \* | \* | \* | 6 |
| Rovin, 2012 (12) |  | \* | \* | \* | \* | \* | \* | 6 |
| Zhang, 2015 (24) |  | \* | \* | \* | \* | \* | \* | 6 |