





		EMLc	ATC codes: L04AB04
Indication	Axial spondyloarthritis	ICD11 code: FA92.OZ	
INN	Adalimumab		
Medicine type	Biological agent		
List type	Complementary		
Additional notes	EML: certolizumab pegol, etanercept, golimumab and infliximab are alternatives, including quality-assured biosimilars. EMLc: etanercept and infliximab are alternatives, including quality-assured biosimilars.		
Formulations	Parenteral > General injections > SC: 40 mg per 0.8 mL ; 40 mg per 0.4 mL		
EML status history	First added in 2019 (TRS 1021)		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	certolizumab pegol (ATC codes: L04AB05) etanercept (ATC codes: L04AB01) golimumab (ATC codes: L04AB06) infliximab (ATC codes: L04AB02)		
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org  Read more about patents. 		
Tags	Biosimilar		
Wikipedia	Adalimumab 		
DrugBank	Adalimumab 		

Expert Committee recommendation

The Committee recognized that these auto-immune disorders are highly debilitating and that there is a public health need for effective treatments for patients who do not respond adequately to first-line treatments (e.g. methotrexate). The Expert Committee recommended the addition of adalimumab with a square box to the complementary list of the EML and EMLc for the second-line treatment of severe chronic inflammatory autoimmune disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease) on the basis of the positive benefit to harm profile of these medicines. For adult patients, therapeutically equivalent alternatives to adalimumab are limited to etanercept, infliximab, certolizumab pegol and golimumab. For children, therapeutically equivalent alternatives should be limited to etanercept and infliximab. The Committee also recognized that these medicines are associated with a significant budget impact on health systems. However, the availability of several therapeutically equivalent alternatives and the increasing availability of biosimilar products could lead to more market competition. The Committee recognized a potential expansion of the role of the Medicines Patent Pool to biological medicines such as these as an opportunity to facilitate affordable access. Quality-assured available biosimilars of these medicines should also be considered as therapeutically equivalent for procurement purposes. The Expert Committee recommended that WHO take action to facilitate access to these medicines through the WHO pre-qualification programme, and through collaboration with partners such as the Medicines Patent Pool.

Background

The application requested the addition of anti-tumour necrosis factor (TNF) biologic medicines etanercept, infliximab and adalimumab (and biosimilars) to the EML and EMLc and of certolizumab pegol and golimumab to the EML for the treatment of severe chronic inflammatory autoimmune disorders: rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Crohn disease. Anti-TNF biologic medicines had not previously been considered for inclusion on the Model Lists.

Public health relevance

Rheumatoid arthritis (RA) is a chronic autoimmune disease that can affect multiple joints, connective tissues, muscles, tendons and fibrous tissues. It is a chronic disabling condition causing severe pain and deformity. The global prevalence of RA in 2017 was 0.27%. Countries from all income levels are affected (1). Ankylosing spondylitis (AS) is a type of chronic inflammatory arthritis that primarily affects the spine and sacroiliac joints and ligaments. Individuals with AS have increased risk for developing articular and extra-articular manifestations that further compound the negative health outcomes and prognosis (2). The pooled global prevalence of AS has been estimated at 0.18%, with the highest prevalence seen in Europe, North America (3) and in individuals who are human leukocyte antigen (HLA)-B27 positive with a family member with the disease (4). Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease affecting children under the age of 16 years. There are limited epidemiological data for JIA, likely due to lack of standard diagnostic criteria (5, 6). However, recent estimates indicate that the prevalence varies from 3.8 to 400/100 000 and after directly standardizing for age and gender, the pooled prevalence is 70.2 [62.9 to 78.1]/100 000 (6). Crohn disease is a chronic autoimmune disorder characterized by severe inflammation of any part of the gastrointestinal tract, but most commonly occurs in the lower part of the small intestine and the colon. Crohn disease is a lifelong systemic condition with debilitating symptoms that negatively affect an individual's quality of life. Most people will need surgery and/or drug treatment. As such, it is associated with high morbidity, mortality, and substantial costs to the health care system. Although the incidence is the highest in western nations, it is greatly accelerating in Asia, South America and Africa (7). The overall burden of Crohn disease remains high with prevalence exceeding 0.3% in North America, Oceania, and many countries in Europe (7). The prevalence has especially risen in the paediatric population in the past 15 years (8).

Benefits

Early RA A systematic review of 16 RCTs (6908 participants) compared anti-TNF biologics to conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) as monotherapy (n=13) or combination therapy (n=3). One RCT compared TNF and non-TNF biologic therapies. The majority of the included studies were rated as medium risk of bias (ROB) (9). Overall, the results of a network meta-analysis revealed that when anti-TNF biologics were combined with methotrexate (MTX), patients achieved higher response rates (as measured by ACR50 (50% change in RA activity measures)) compared to MTX alone: ETN + MTX relative risk (RR) 1.49, 95%CI 1.27 to 1.74; moderate strength of evidence; ADA + MTX RR 1.35, 95%CI 1.15 to 1.59; low strength of evidence; CZP + MTX RR 1.20, 95%CI 1.04 to 1.38; low strength of evidence; IFX + MTX RR 1.57, 95%CI 1.30 to 1.88; insufficient strength of evidence (9). Results also indicated that the combination of anti-TNF biologics plus MTX were favoured in comparison to biologic monotherapy. The ACR50 response rate was significantly higher for ADA + MTX than ADA monotherapy (RR 1.52, 95%CI 1.28 to 1.80; moderate evidence) and ETN + MTX than ETN monotherapy (RR 1.57, 95%CI 1.23 to 2.02)(9). Anti-TNF combinations were also associated with benefits compared to MTX monotherapy for the outcome measures of remission, radiographic changes or functional capacity (9). Advanced RA A systematic review of 98 RCTs evaluated the comparative efficacy of different treatment options for advanced RA. Of these, 61 studies were included to determine the efficacy of anti-TNF biologics. Of the 88 studies assessed for risk of bias, half were judged to have a high ROB and only 10 were considered to have a low ROB overall; the rest (39%) had an unclear ROB overall (10). ETN + MTX (odds ratio (OR) 3.95, 95% credible interval (CrI) 2.29 to 7.51), IFX+ MTX (OR 3.00, 95%CrI 1.78 to 5.08), ADA+ MTX (OR 3.99, 95%CrI 2.84 to 5.62), CZP + MTX (OR 5.35, 95%CrI 3.42 to 8.67) and GOL + MTX (OR intravenous (IV) 2.90, 95%CrI 1.21 to 7.12; OR subcutaneous (SC) 6.00, 95%CrI 3.27 to 11.35) all produced greater ACR 50 responses when compared to MTX monotherapy. Anti-TNF biologics in combination with MTX were also associated with greater odds of achieving ACR 50 response compared to MTX in combination with another conventional synthetic disease-modifying antirheumatic drug (csDMARD). With the exception of Infliximab, all the anti-TNF biologics in combination with MTX produced a comparable ACR 50 response to csDMARD triple therapy (10). There were no significant differences in radiographic progression for any anti-TNFs in combination with MTX compared to csDMARD double or triple therapy. There were statistically significant

higher odds of achieving remission among those who were treated with anti-TNF biologics in combination with MTX compared to MTX. Anti-TNF biologics in combination with MTX also produced more favourable odds of remission compared to a csDMARD plus MTX (10). CZP + MTX, achieved a statistically significant improvement in the DAS28 (Disease Activity Score 28) compared to MTX monotherapy. IFX, ADA, CZP and GOL (IV and SC) all in combination with MTX produced a significantly lower disability score and higher physical health-related quality of life scores compared to MTX monotherapy. Intravenous GOL and CZP both in combination with MTX produced higher mental health-related quality of life than MTX. Patients treated with ETN, ADA or CZP all in combination with MTX had lower pain scores than MTX monotherapy. CZP + MTX produced a significantly lower fatigue score than MTX monotherapy (10).

Ankylosing spondylitis A systematic review of 21 short-term RCTs involving 3308 participants assessed the benefits and harms of anti-TNF biologics in comparison with placebo, other drugs or usual care in the treatment of AS. Most included studies had low or unclear risk of bias (4). Patients receiving anti-TNF biologics were found to be three to four times more likely to achieve an Assessment in SpondyloArthritis International Society (ASAS) 40 response by six months compared to placebo (ETN RR 3.31, 95%CrI 2.38 to 4.53; IFX RR 4.07, 95%CrI 2.80 to 5.74; ADA RR 3.53, 95%CrI 2.49 to 4.91; GOL RR 2.90, 95%CrI 1.90 to 4.23) (high strength of evidence). The number needed-to-treat (NNT) to receive this response ranged from 3 to 5. No significant difference was found for ASAS 40 response between the anti-TNF biologics (4). Moderate strength evidence found that patients receiving anti-TNF biologics were also significantly more likely than placebo to achieve ASAS partial remission. The NNT to detect a minimally clinically important difference of 0.7 points for physical functioning ranged from 2 to 4. There was high strength evidence that ETN, IFX, ADA and GOL all had significantly lower BASFI (Bath Ankylosing Spondylitis Functional Index) scores compared to placebo. Low to moderate strength evidence suggested that anti-TNF biologics have a small impact on reducing spinal inflammation, however the clinical relevance of this was not clear (4).

Juvenile idiopathic arthritis A systematic review of 100 full-text articles and conference abstracts (67 RCTs) evaluating the efficacy and safety of interventions for JIA included eight RCTs comparing anti-TNF biologics (11). This review found that patients receiving ETN 0.4 mg/kg were more likely to maintain a disease response measured by the American College of Rheumatology (ACR) Pediatric (PEDI) 30 compared to patients receiving placebo (RR 1.91, 95%CrI 1.28 to 2.59). No other anti-TNF biologics showed statistically significant differences compared to placebo for this outcome. There were no significant differences between anti-TNF biologics and methotrexate in combination with placebo. Indirect estimates of the head-to-head comparisons of anti-TNF biologics did not demonstrate statistically significant differences (11). The number of active joints decreased for 0.2 mg/kg and 0.4 mg/kg ETN (mean difference (MD) -11.23, 95%CrI -18.16 to -4.59 and MD -11.01, 95%CrI -14.59 to -7.52, respectively) and the number of joints with limited range of motion decreased for 0.4 mg/kg ETN only (MD -5.15, CrI -9.5 to -0.8) (11).

Crohn disease A systematic review comparing the efficacy of therapies for induction and maintenance of remission in adult patients with Crohn disease included 15 trials involving anti-TNF therapies (IFX: one for induction and two for maintenance; ADA: four for induction and three for maintenance; CZP: four for induction and one for maintenance) and five additional studies evaluating combination therapies with IFX (12). All but one study assessed remission using the Crohn Disease Activity Index (CDAI) less than 150. Most of the included studies were assessed to have unclear risk of bias. Other limitations of this study have been identified in the literature that may limit the applicability of the results (13). However, additional network meta-analyses have found similar effectiveness of anti-TNFs against placebo in the induction and maintenance of remission for Crohn disease even after accounting for these differences (14-16). Compared to placebo, IFX (odds ratio (OR) 2.8, 95%CrI 1.4 to 7.2), IFX plus azathioprine (OR 4.3, 95%CrI 2.0 to 9.8) and ADA (OR 2.9, 95%CrI 1.6 to 5.5) all had over 99% probability of being superior at inducing remission in Crohn patients. These same drugs also proved to be superior to azathioprine/6-mercaptopurine (OR 2.3, 95%CrI 1.3 to 5.0, OR 3.4, 95%CrI 1.9 to 6.3, and OR 3.4, 95%CrI 1.9 to 6.3). IFX plus azathioprine was 2.7 times more likely to induce remission compared to methotrexate (95%CrI 1.9 to 6.3). IFX + azathioprine (OR 3.1, 95%CrI 1.4 to 7.7) and ADA (OR 2.1, 95%CrI 1.0 to 4.6) were found to be superior to CZP for inducing remission (12). For maintenance of remission, IFX (OR 2.8, 95%CrI 1.8 to 4.5), IFX plus azathioprine (OR 5.2, 95%CrI 2.8 to 11), ADA (OR 5.1, 95%CrI 3.3 to 8.1) and CZP (OR 2.0, 95%CrI 1.4 to 3.0) all had over 99% probability of being superior to placebo. ADA (OR 2.9, 95%CrI 1.6 to 5.1), IFX (OR 1.6, 95%CrI 1.0 to 2.5) and IFX plus azathioprine (OR 3.0, 95%CrI 1.7 to 5.5) all had greater odds at achieving maintenance of remission compared to azathioprine/6-mercaptopurine. IFX + azathioprine (OR 2.6, 95%CrI 1.3 to 6.0) and ADA (OR 2.5, 95%CrI 1.4 to 4.6) were found to be superior to CZP for maintenance of remission. IFX plus azathioprine was superior to IFX monotherapy for maintenance of remission (OR 1.8, 95%CrI 1.0 to 3.8) (12).

A systematic review comparing efficacy of pharmacologic interventions for preventing relapse of Crohn disease after surgery found that anti-TNF monotherapy was the most effective therapy for post-operative prophylaxis, with large effect sizes relative to all other strategies including antibiotics, immunomodulator monotherapy, immunomodulators with antibiotics, budesonide (clinical relapse: RR, 0.02 to 0.20; endoscopic relapse: RR, 0.005 to 0.04) (17).

Harms

Uncommon yet serious adverse events for anti-TNF biologics include serious infection, malignancy and lymphoma, neurologic effects and cardiac failure. A 2011 Cochrane Systematic Review assessed the potential adverse effects of anti-TNF biologics: etanercept (39 RCTs), infliximab (40 RCTs), adalimumab (22 RCTs), certolizumab pegol (six RCTs) and golimumab (eight RCTs) alone or in combination with other therapies. This review found that compared to control, CZP was associated with a higher odds of serious adverse effects (OR 1.57, 95%CI 1.06 to 2.32) and serious infections (OR 4.75, 95%CI 1.52 to 18.45) and IFX was associated with higher odds of total adverse events (OR 1.55, 95%CI 1.01 to 2.35) and withdrawals due to adverse events (OR 2.34, 95%CI 1.40 to 4.14) (18).

Early RA The network meta-analysis for early RA found no significant differences in serious adverse events or discontinuations attributable to adverse events between MTX monotherapy and any of the anti-TNF biologics (low strength of evidence). IFX + MTX also did not differ from csDMARD combination therapies (low strength of evidence). Anti-TNF therapy with a csDMARD did not differ significantly in serious adverse events or discontinuations attributable to adverse events compared to TNF biologic monotherapy (moderate strength of evidence) (9).

Advanced RA The systematic review for advanced RA found that there were no significant differences in serious adverse events or withdrawals attributable to adverse events between the anti-TNF biologics in combination with MTX and MTX monotherapy. ETN + MTX had lower odds of withdrawals attributable to adverse events compared to a csDMARD in combination with MTX (OR 0.33, 95%CrI 0.11 to 0.89). There was insufficient evidence to detect any differences in anti-TNF treatment comparisons for mortality, serious infections, tuberculosis, cancer, leukaemia, lymphoma, congestive heart failure, major adverse cardiac events and herpes zoster. A pairwise meta-analysis found no statistically significant difference in mortality for IFX + MTX and MTX monotherapy. Additional pairwise meta-analyses found that there were no differences in serious infections for patients treated with the ETN, IFX or GOL (plus MTX) versus MTX alone. There was insufficient evidence for this outcome for ADA + MTX. A pooled estimate from two trials comparing ETN monotherapy and MTX combination therapy, found that there were no significant differences in cancer, and a pairwise meta-analysis found no significant differences between IFX + MTX and MTX groups (10).

Ankylosing spondylitis Pooled results for all anti-TNF biologics demonstrated a moderate level of evidence that there is an increased risk of withdrawals due to adverse events compared to placebo (Peto OR 2.44, 95%CI 1.26 to 4.72), with an absolute increase of 1% (95%CI 0% to 2%). There was no difference in risk for serious adverse events (Peto OR 1.45, 95%CI 0.85 to 2.48). ETN (25 and 50 mg) was the only anti-TNF biologic that had an individual increase in withdrawals due to adverse events versus placebo (RR 3.65, 95%CI 1.27 to 11.79) with an absolute increased harm of 2% (95%CrI 0.2% to 8%). The effect of ETN compared to placebo for serious adverse events was uncertain. There was uncertainty reported for adverse effects or withdrawals due to adverse effects between either ADA, GOL or IFX and placebo. The strength of evidence was moderate for all safety outcomes (4).

Juvenile idiopathic arthritis The systematic review for JIA found that biologics were safe in short-term use among both polyarticular course and active systemic patients. For polyarticular course, one RCT found that no serious adverse effects or withdrawals due to adverse effects occurred for high or low doses of ETN. Another RCT found no withdrawals due to adverse events occurred for ADA with or without methotrexate and few withdrawals due to adverse events (11).

Crohn disease IFX + azathioprine (OR 0.27, 95%CrI 0.08 to 0.72) and ADA monotherapy (OR 0.43, 95%CrI 0.26 to 0.69) were associated with significantly lower odds of total withdrawals compared to placebo. Similarly, IFX + azathioprine was associated with significantly lower odds of total withdrawals compared to Azathioprine/6-mercaptopurine (OR 0.39, 95%CrI 0.14 to 0.98) and methotrexate (OR 0.29, 95%CrI 0.07 to 0.93) (12). For withdrawals due to adverse events, IFX (OR 2.7, 95%CrI 1.6 to 4.7) and IFX + azathioprine (OR 3.2, 95%CrI 1.6–6.1) had significantly greater odds of withdrawals due to adverse events compared to placebo. Adalimumab had over a 99% probability of having less withdrawals due to adverse events than placebo (OR 0.48, 95%CrI 0.31 to 0.74). CZP (OR 0.23, 95%CrI 0.13 to 0.40) and ADA (OR 0.12, 95%CrI 0.06 to 0.24) had significantly less odds of withdrawals due to adverse events compared to azathioprine/6-mercaptopurine and methotrexate (CZP: OR 0.07, 95%CrI 0.01 to 0.28 and ADA: OR 0.04, 95%CrI 0.00 to 0.16). Infliximab monotherapy had significantly lower odds of withdrawals due to adverse events compared to methotrexate (OR 0.21, 95%CrI 0.02 to 0.93) (12). Anti-TNF comparisons indicated that ADA (OR 0.0, 95%CrI 0.24 to 0.96) and IFX + azathioprine (OR 0.32, 95%CrI 0.09 to 0.94) have significantly lower odds of total withdrawals than CZP. ADA had lower odds of withdrawals due to adverse events than CZP (OR 0.55, 95%CrI 0.32 to 0.93) and IFX (OR 0.18, 95%CrI 0.09 to 0.34). IFX + azathioprine (OR 3.6, 95%CrI 1.7 to 7.5) and IFX monotherapy (OR 3.1, 95%CrI 1.7 to 5.8) had significantly greater odds of withdrawals due to adverse events than CZP. IFX + azathioprine also had greater odds than ADA of withdrawals due to adverse events (OR 6.5, 95%CrI 3.0 to 14) (12).

Cost / cost effectiveness

The application presented details of available information on drug costs for the anti-TNF biologics from Australia, Canada, the United Kingdom and the United States. These medicines are associated with a significant budget impact to health systems due to both price and volume of use. In addition, the application identified and summarized the findings numerous economic evaluations conducted primarily in Canada, the United Kingdom and the United States involving anti-TNF biologics for the indications proposed for EML listing (19–35).

WHO guidelines

None available.

Availability

These medicines have wide marketing approval globally. Biosimilars are available for ETN, IFX and ADA

Other considerations

The Committee noted that most of the evidence presented in the application comes from countries with low levels of tuberculosis and/or hepatitis B infection. Reactivation of latent tuberculosis infection and hepatitis B in patients receiving anti-TNF biologics has been reported (36, 37), and this risk should be taken into consideration when anti-TNF biologics are considered in settings where there is a higher burden of TB and hepatitis B

1. GBD Results Tool | GHDx. 2018 [website]. Seattle: Institute for Health Metrics and Evaluation, University of Washington; 2018. (<http://ghdx.healthdata.org/gbd-results-tool>, accessed 29 September 2019).
2. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(1):65–73.
3. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res (Hoboken)*. 2016;68(9):1320–31.
4. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev*. 2015(4):CD005468.
5. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis why does it vary so much? *J Rheumatol*. 2002;29(7):1520–30.
6. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine*. 2014;81(2):112–7.
7. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of populationbased studies. *Lancet*. 2018;390(10114):2769–78.
8. Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. *Am J Gastroenterol*. 2017;112(7):1120–34.
9. Donahue KE, Gartlehner G, Schulman ER, Jonas B, Coker-Schwimmer E, Patel SV et al. AHRQ Comparative Effectiveness Reviews. Drug Therapy for Early Rheumatoid Arthritis: A Systematic Review Update. Rockville: Agency for Healthcare Research and Quality (US); 2018.
10. Wells GA, Smith C, Hossain A, Karsh J, Singh J, Hazlewood G et al. CADTH Health Technology Assessments. Drugs for the Management of Rheumatoid Arthritis: Clinical Evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2018.
11. Smith C. Efficacy and Safety of Pharmacological and Non-Pharmacological Interventions in Juvenile Idiopathic Arthritis: A Series of Systematic Reviews and Network Meta-Analyses (Doctoral dissertation). Ottawa: Université d'Ottawa/University of Ottawa; 2017. Available from https://ruor.uottawa.ca/bitstream/10393/35744/1/Smith_Christine_2017_thesis.pdf, accessed 29 September 2019.
12. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015;148(2):344–54.e5; quiz e14–5.
13. Bonovas S, Moja L, Danese S. In the Presence of Conceptual Heterogeneity, Results of Network Meta-analysis Comparing Therapies in Crohn's Disease Need to Be Interpreted With Caution. *Gastroenterology*. 2015;148(7):1483–4.
14. Singh S, Fumery M, Sandborn WJ. Systematic review and network meta-analysis: first- and secondline biologic therapies for moderate-severe Crohn's disease. 2018;48(4):394–409.
15. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV, Jr. Comparative efficacy of biologic therapy in biologic-naive patients with Crohn disease: a systematic review and network metaanalysis. *Mayo Clin Proc*. 2014;89(12):1621–35.
16. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther*. 2014;39(12):1349–62.
17. Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV, Jr. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. *Gastroenterology*. 2015;148(1):64–76.e2; quiz e14.
18. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011(2):CD008794.

19. Curtis JR, Chastek B, Becker L, Quach C, Harrison DJ, Yun H et al. Cost and effectiveness of biologics for rheumatoid arthritis in a commercially insured population. *J Manag Care Spec Pharm.* 2015;21(4):318–29.
20. Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordstrom D, Blom M. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. *PLoS One.* 2015;10(3):e0119683.
21. van der Velde G, Pham B, Machado M, Ieraci L, Wittman W, Bombardier C et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken).* 2011;63(1):65–78.
22. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technol Assess.* 2011;15(14):1–278.
23. Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess.* 2006;10(42):iii-iv, xi-xiii, 1–229.
24. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. *Arthritis Rheum.* 2008;58(4):939–46.
25. Liu Y, Wu EQ, Bensimon AG, Fan CP, Bao Y, Ganguli A et al. Cost per responder associated with biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis. *Adv Ther.* 2012;29(7):620–34.
26. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E et al. Tumour necrosis factor-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2016;20(9):1-334, v–vi.
27. McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11(28):1-158, iii–iv.
28. Kirchhoff TD, Mittendorf T, Schmidt RE, Jablonka A, Merkesdal S. Cost-effectiveness of TNF-alpha inhibition in active ankylosing spondylitis: a systematic appraisal of the literature. *Expert Rev Pharmacoecon Outcomes Res.* 2012;12(3):307–17.
29. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. *Arthritis Care Res (Hoboken).* 2011;63(1):111–9.
30. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2016;20(34):1–222.
31. Huoponen S, Blom M. A Systematic Review of the Cost-Effectiveness of Biologics for the Treatment of Inflammatory Bowel Diseases. *PLoS One.* 2015;10(12):e0145087.
32. Dretzke J, Edlin R, Round J, Connock M, Hulme C, Czczot J et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. *Health Technol Assess.* 2011;15(6):1–244.
33. Beilman CL, Kirwin E, Ma C, McCabe C, Fedorak RN, Halloran B. Early Initiation of Tumor Necrosis Factor Antagonist-Based Therapy for Patients With Crohn's Disease Reduces Costs Compared With Late Initiation. *Clin Gastroenterol Hepatol.* 2018.
34. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther.* 2009;30(3):265–74.
35. Blackhouse G, Assasi N, Xie F, Marshall J, Irvine EJ, Gaebel K et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. *J Crohn's Colitis.* 2012;6(1):77–85.
36. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf.* 2016;15(sup1):11–34.
37. Watanabe T, Fukae J, Fukaya S, Sawamukai N, Isobe M, Matsushashi M et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis.* 2019;22(4):574–82.

