Leveling the Field in Canada

Moving Toward Reimbursement Equality
in Biologic Therapy for
Canadians with Rheumatoid Arthritis

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1. Overview

The primary objective of this paper is to provide rationale to allow specialist physicians to prescribe the biologic therapy most suited for an individual rheumatoid arthritis (RA) patient whenever it is recognized that the particular biologic would provide the best possible outcome for the patient. The secondary objective is to highlight to government decision-makers in this country the lack of equitable access and patient/physician choice in treating RA with the biologics.

Rheumatoid arthritis is the most severe form of progressive arthritis and occurs in between 400,000 to 600,000 Canadian adults. Biologics are the standard of care worldwide for the treatment of patients with severe RA. However, no one biologic therapy is effective in all RA patients. While the long-term use of biologics has proven them efficacious and safe, as demonstrated by numerous clinical studies and as well-described in evidence-based guidelines, there are some differences in the adverse event profiles which must be balanced against the risk of untreated disease.

The biologics have proven efficacy in the treatment of early rheumatoid arthritis, Methotrexate inadequate responders and tumor-necrosis factor inhibitors inadequate responders.

Currently, the majority of biologics available for the treatment of RA in Canada are available only on a case-by-case basis in most of the provinces and territories through their public formularies. However, there are distinct differences as to which biologics can be administered for the treatment of RA and under what circumstances treatment can be provided. The results are unequal patient access to biologics for RA across this country and a lack of choice for patients and their physicians in treating this disease.

The challenge: delivering the most effective rheumatoid arthritis treatment to patients in Canada

a. Public reimbursement inequities in rheumatoid arthritis treatment with biologics

- Not all biologics approved for RA treatment are listed on all public formularies. This inequity must be corrected.
- Regardless of whether all biologics are listed on a particular public formulary, there are often unreasonable restrictions that prevent RA patients from receiving the most effective treatment.

Recommendation: That if there is evidence of a fair response, but one not quite meeting the criteria set by the clinical outcome measures, an extension for re-assessment of response at six months be permitted.

b. Choice of biologics in rheumatoid arthritis treatment and public reimbursement

- To provide the most effective treatment, the treating physician, in discussion with the RA patient, must be permitted the choice to prescribe the most appropriate biologic for that individual.
- For those who respond, this results in a return to a "full life" for that person living with RA.

Research supports public formulary policy that allows for the specialist physician to prescribe the right biologic to the right person at the right time.

Recommendation: That if a patient has been deemed initially eligible for a biologic, there should be a seamless process when switching to a second or third biologic (if needed) without the necessity of repeating the initial formal application and clinical pro forma.

c. Expert input into public reimbursement of biologics in rheumatoid arthritis treatment

- Specialist physicians can provide the appropriate prerequisites for the use of biologics in rheumatoid arthritis, including the development of specific criteria for each medication and within the case-by-case request process.
- An open communication process must be developed to ensure that comprehensive information is available to public formulary decision-makers.
- This results in the best quality of patient care, delivered in a cost-effective manner.

Recommendation: That the provincial and territorial governments seek advice from rheumatologists through a formal advisory framework in determining indication prerequisites.

Recommendation: That some form of appeal mechanism be set up that is satisfactory to patients, physicians, and government to review both approval applications for general approval of a specific drug as well as the needs of specific patients where required.

Biologic Therapies Reimbursement Rating	Province	Detailed Remarks
Good	**BC** **SK**	• Provides Special Authority reimbursement for 5 out of 7 biologic therapies approved by Health Canada for use in rheumatoid arthritis. • Least restrictive Special Authority reimbursement criteria (e.g. fewest other medication failures required, and no interference in prescribing order). • Shortest wait times for initial processing of Special Authority reimbursement applications. • Fewest number of Special Authority reimbursement renewal applications required. • Formal or informal appeal mechanism in place for Special Authority reimbursement coverage denials.
Average	**AB** **ON** **QC** **NB** **NS**	• Provides Special Authority reimbursement for 5 out of 7 biologic therapies approved by Health Canada for use in rheumatoid arthritis. • Somewhat restrictive Special Authority reimbursement criteria (e.g. other medication failures required, some interference in prescribing order). • Longer wait times for initial processing of Special Authority reimbursement applications. • Special Authority reimbursement renewal applications required before one full year of coverage expires. • No transparent appeal mechanism in place for Special Authority reimbursement coverage denials.
Poor	**MB** **NFLD** **NIHB** **NT** **NU** **PEI** **YT**	• Provides Special Authority reimbursement for 4 out of 7 biologic therapies approved by Health Canada for use in rheumatoid arthritis. • Overly restrictive Special Authority reimbursement criteria (e.g. other medication failures required, interference in prescribing order). • Longest wait times for initial processing of Special Authority reimbursement applications. • Special Authority reimbursement renewal applications required before one full year of coverage expires. • No appeal mechanism in place for Special Authority reimbursement coverage denials.

2. Introduction

RA is a debilitating autoimmune disease that most often affects people in the prime of their lives (20-50 years of age), but can manifest at any age. RA progressively erodes the synovial joints and surrounding tissues and if left untreated, causes irreversible joint damage, chronic pain and losses of function, resulting in profound losses in quality of life (home, social, work) and a decreased life expectancy.[1–7]

Similar to cancer where the goal of treatment is to eradicate the tumor, the goal with RA treatment is to minimize systemic disease activity, thereby preventing joint degradation and minimizing the risk of other serious comorbidities such as heart disease and stroke. What is clear is the need for early intervention in patients with confirmed RA to preserve joint function.[5-7] For example, in one study using even a weak anti-rheumatic agent, hydroxychloroquine, delay in initiation of this drug led to increased joint damage still evident years later.[5]

Methotrexate (MTX) is the anchor for modern management of RA. While many RA patients do respond to methotrexate monotherapy, as many as a third do not (inadequate responders, IR) or have short-term control before regressing back to an active disease state. Furthermore, methotrexate in full, required dosage can, in some patients, be impossible to tolerate because of side effects.

The biologics are therapies that have been engineered to target and block specific disease pathways responsible for the joint destruction characteristic of RA.[8] The biologics have provided tremendous advances in RA management with many patients experiencing complete clinical control of RA and cessation of progressive joint damage, both in early RA or in those who are inadequate responders to traditional disease modifying anti-rheumatic drugs, including methotrexate. Two general sub-classes of the biologics are recognized: the anti-tumor necrosis factor inhibitor biologics (etanercept, infliximab, adalimumab, golimumab and certolizumab) and the non-anti-tumor necrosis factor inhibitors biologics (anakinra, abatacept, rituximab and tocilizumab). The current biologics are a related class, having in their targeted approach, a complex synthetic requirement. Thus, each individual drug, before consideration for approval, requires clinical testing and proof of clinical efficacy. Unlike simpler chemicals, having a structure seemingly similar to a known agent (bio-similar) is by itself insufficient to demonstrate either efficacy or safety.

3. Public reimbursement inequities in rheumatoid arthritis treatment with biologics

According to the Oxford Canadian Dictionary, discrimination is defined as 'an act or policy of unfavourable treatment based on prejudice'. Many different groups face discrimination for a wide variety of reasons – on the basis of age, gender, race, sexual orientation, religion, disability status – and these types of discrimination are generally recognized and understood by the public. What is less often acknowledged is that people living with certain diseases frequently face unfair, unequal treatment based on the type of disease they have. Arthritis is one of those diseases.

Quite simply, people who are living with rheumatoid arthritis face discrimination on a daily basis.

It occurs on many different levels—from a friend refusing to believe a child can have arthritis, to an employer refusing to modify a workspace, to one level of government refusing to pay for the treatments approved by a different level of government.

The discrimination that people with arthritis are facing, day in and day out, can feel like it comes from every direction. Negative effects of discrimination against people with arthritis range from feelings of loneliness and isolation, to unemployment and poverty, to disability, joint destruction, and even death.

4. Choice of biologics in rheumatoid arthritis treatment and public reimbursement

The use of biologics is deemed appropriate in those patients with RA in whom therapeutic prerequisites have been met and where the rheumatologist and the patient have agreed an approach with a biologic is desirable.

All of the evidence to date generally supports the impression that there is little difference among the biologics in regards to efficacy in RA management, so comparative efficacy should have little bearing on the therapy chosen[8–10]. When weighing the decision of which specific biologic to utilize the clinician should engage the patient in discussion regarding differences in access (publicly or privately funded), administration (intravenous, subcutaneous), and safety (adverse events, serious adverse events, infection, malignancies) among this class of medications with specific consideration of the patient's unique clinical profile including disease duration and pertinent comorbidities.

Choice of biologics should be a shared decision between physician and patient based on the patient's specific disease characteristics preferences and with reflection of his/her co-morbidities and specific risks.

5. Efficacy of the biologic agents for the treatment of rheumatoid arthritis

There are no randomized, head-to-head trials comparing any of the biologic therapies to one another; thus, no definitive rankings of the agents based on efficacy or safety are possible. Further, sophisticated statistical analyses and systematic reviews have concluded that there are no significant differences amongst the currently used biologics in terms of efficacy[8–13].

The efficacy and safety of specific biologics are generally investigated in one of three patient groups: those with early RA, those who are Methotrexate inadequate responders, and those who are inadequate responders to anti-tumor-necrosis factor inhibitors. Clinical efficacy is typically monitored by the use of assessment scales (eg. American College of Rheumatology scales or the Disease Activity Score) and by assessment of damage by X-ray (eg. Sharp's score). The efficacy measures (i.e. American College of Rheumatology 20, 50, and 70 responses at six months) are essentially similar among the biologics in both early RA patients naïve to methotrexate (70%, 60% and 45%, respectively) and in those who have responded inadequately to methotrexate (methotrexate inadequate responders) (60%, 40% and 20%, respectively).[11, 14–40]

a. Efficacy of the biologic agents for the treatment of early rheumatoid arthritis

The effective treatment of RA as early as possible after positive diagnosis is critical to preserve joint integrity since it is documented that joint damage begins within six weeks of RA initiation. The biologics have exhibited significant clinical benefit in the treatment of early RA (i.e. methotrexate naïve patients) and, where assessed, the use of a biologic therapy together with methotrexate has been better than the biologic or methotrexate alone[11, 14–18, 21,38, 39, 42–45]. These findings demonstrate the potential for the use of biologics and methotrexate early in the disease progression to maintain function and avoid disability.

For the preservation of joint health, treatment for RA should be initiated as close to diagnosis as possible

b. Efficacy of the biologic agents for the treatment of methotrexate inadequate responders patients

While methotrexate is undeniably a key component of the armamentarium to treat RA, there are a large proportion of patients who have an inadequate response to methotrexate as monotherapy or in combination with other disease modifying anti-rheumatic drugs. In those who have responded inadequately to methotrexate, anti-tumor necrosis factor inhibitors have been demonstrated to be significantly more efficacious in improving the clinical signs and symptoms of RA than methotrexate alone[19–22]. The durability of anti-tumor necrosis factor inhibitor response is good in such patients, although some national

registries suggest there may be differences among the different medications. Follow-up in open-label extensions has, with some medications, been up to ten years with no new safety concerns becoming evident.

Successful treatment of methotrexate inadequate responder patients has also been reported with non-tumor-necrosis factor inhibitors biologics[28–32, 45–47]. Similar to what is observed in early RA, in the majority of trials with biologic treatment a better response is attained with the combination of Methotrexate and the biologic as compared to either alone.

c. Efficacy of the biologic agents for the treatment of tumor-necrosis factor inhibitors inadequate responder patients

While most patients respond to tumor-necrosis factor inhibitors, there are still many others that do not obtain a satisfactory response with their first biologic (commonly tumor-necrosis factor inhibitors). Sometimes loss of efficacy may reflect the development of antibodies to the agent used. All of the available non-tumor-necrosis factor inhibitor biologics have proven efficacy in the treatment of those patients responding inadequately to anti-tumor necrosis factor inhibitors[33, 34, 36, 38, 41, 48, 49]. Thus, the failure of one biologic should not be regarded as a loss of effect for the class, as other biologics with different mechanisms of action often elicit a positive clinical response.

d. Sequential use and combined use of biologic therapies

There is no definite proof (i.e. randomized control trial data) that supports the switching of one anti-tumor necrosis factor inhibitor to another in the case of a failure to respond to the first, whether primary or secondary. There is, nevertheless, a large amount of clinical registry data suggesting that this type of switching may be effective, although there may be some reduced adherence and effectiveness with the second biologic agent[50.] Thus, clinical experience has proved this to be a feasible alternative. Further, recent randomized control trial evidence has demonstrated the efficacy of one anti-tumor-necrosis factor inhibitor antibody in the treatment of patients responding poorly to a previous, different anti-tumor necrosis factor inhibitor[37]. There have been no increased risks associated with sequential use of different biologics, whether of the same class or a different one. Thus anti-tumor necrosis factor inhibitors can safely follow rituximab or abatacept and vice-versa. Several attempts at combined use of biologics have been associated with an increased safety risk and this approach should be avoided[51, 56, 57].

There are no increased concerns of adverse events with sequential use of biologics

6. Biologic agents and adverse events

When considering a specific biologic for a specific patient a clinician must weigh the biologic's specific benefit with the perceived risk. These infrequent adverse events need to also be balanced with the risk of untreated disease. With the anti-tumor necrosis factor inhibitors, there are data suggesting increased adverse event incidence as compared with methotrexate monotherapy[9, 16, 52–57]. Thus, while infections may be increased, particularly with higher doses, some anti-tumor necrosis factor inhibitors are less likely than others to be associated with "opportunistic" infections (i.e. tuberculosis, listeria, fungi). To date, registry data do not support an increased incidence of neoplasia, including lymphoma, except for a small increase in the risk of non-melanoma skin cancers, which are considered an acceptable risk. Longer follow-up in registries and open-label extensions have not shown safety concerns with tumor-necrosis factor inhibitors to increase with time, but rather the reverse.

With respect to the non-anti-tumor necrosis factor inhibitors, there has been no evidence to suggest that the use of anti-tumor necrosis factor inhibitors prior to or following other non-anti-tumor necrosis factor inhibitors (i.e. abatacept, rituximab, tocilizumab) affects safety and in fact the reverse is true. A biologic with a different mechanism of action can immediately follow anti-tumor necrosis factor inhibitors[36] or after some time has elapsed without undue concerns for safety.

It is clear that the risk of infection is increased with the concomitant use of glucocorticoids; one aim in treating patients with RA is to discontinue prednisone or use the lowest dose possible.

7. Damage to joints over time as assessed by X-ray

The slowing or arrest of X-ray damage is one of the new benchmarks for RA therapies, as preservation of joint structure has been demonstrated to significantly decrease the chances of permanent disability. Treatment with biologics has demonstrated a cessation or slowing of radiographic damage after therapy for as long as five years in the majority of treated patients[11, 12, 14–18, 22, 25, 27, 29, 31, 32, 34, 35, 40–43, 46, 58, 62]. X-rays over time prove that biologics are the most efficacious therapy for the treatment for patients with RA.

X-rays over time prove that biologics are the most efficacious therapy for the treatment for patients with RA and because of this have become the global standard of care for progressive RA

8. Expert input into public reimbursement of biologics in rheumatoid arthritis treatment

The process in British Columbia illustrates how experts can provide valuable and effective input into public reimbursement of biologics for RA. Through the Rheumatoid Arthritis Drug Benefit Adjudication Advisory Committee, an individual application for a biologic for RA is reviewed by a rheumatologist and a recommendation to BC PharmaCare is made as to whether to provide that medication through public funding. The Rheumatoid Arthritis Drug Benefit Adjudication Advisory Committee also provides advice to the government on difficult compassionate/exceptional cases or new cases, and helps develop criteria. Although their work is strictly advisory in nature, their adjudications have been consistently followed by BC PharmaCare.

9. Summary and Recommendations

Biologics as a group are highly effective in the treatment of RA being efficacious in early RA, methotrexate inadequate responders, and tumor-necrosis factor inhibitor inadequate responder patients[63]. With the biologics, there are some concerns of increases in infection and adverse events, particularly with higher doses, but these risks need to be weighed for each individual against the potential benefit. More often than not, the biologics preserve and often enhance quality of life and function to RA patients.

There are well-described evidence-based guidelines for the treatment of RA[13, 63, 64]. In the absence of properly defined head-to-head studies it is impossible to state that any given biologic is better than any other. Efficacy measures at six months are similar with all agents when used in similar patients (eg. those with early RA, poor response to Methotrexate or to an anti-tumor-necrosis factor inhibitors agent). Yet, clear reasons for preferring one class or one drug over another at a given point may exist for an individual patient and physicians should be provided the latitude to select which drug to start with and which to switch to, based on a consensus with the patient given their preferences and overall status, including co-morbid conditions.

Response to biologic agents is commonly assessed in Canada by clinical outcome measures. While many patients respond quickly to biologics, there are others that do not respond as quickly, but do show significant benefit somewhat later on in the course of therapy. Some 85% of patients who will show such a response have done so by three months but about 15% of late-responders will be missed.

We recommend that if there is evidence of a fair response, but one not quite meeting the criteria set by the clinical outcome measures, an extension for re-assessment of response at six months be permitted.

Earlier treatment of RA has been shown to better maintain function than later treatment of advanced disease. Thus, after stopping one drug for an inadequate response,

it is inappropriate to have to wait for a flare before starting the next course of therapy. We recommend that if a patient has been deemed initially eligible for a biologic, there should be a seamless process when switching to a second or third biologic (if needed) without the necessity of repeating the initial formal application and clinical pro forma.

For anti-tumor necrosis factor inhibitor inadequate responders, the benchmark placebo controlled studies have been with medications offering a different mechanism of action than with anti-tumor necrosis factor inhibitors and it has been clear that they are effective in treating this small group of patients. We recommend that the provincial and territorial governments seek advice from rheumatologists through a formal advisory framework in determining indication prerequisites, as has been done in British Columbia. We also recommend that some form of appeal mechanism be set up that is satisfactory to patients, doctors, and government to both review approval applications for general approval of a specific drug as well as the needs of specific patients where required.

We welcome the increased options that access to all biologics will afford RA patients and their physicians across Canada.

10. Reference List

1 **Pratt AG, Isaacs JD, Mattey DL.** Current concepts in the pathogenesis of early rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2009;23:37-48.

2 **Scott DL.** What have we learnt about the development and progression of early RA from RCTs? Best Pract Res Clin Rheumatol. 2009;23:13-24.

3 **Uhlig T, Loge JH, Kristiansen IS, Kvien TK.** Quantification of reduced health-related quality of life in patients with rheumatoid arthritis compared to the general population. J Rheumatol. 2007;34:1241-1247.

4 **Sokka T, Abelson B, Pincus T.** Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol. 2008;26:S35-S61.

5 **Tsakonas E,Fitzgerald AA, Fitzcharles MA, et al.** Consequences of delayed therapy with second-line agents in rheumatoid arthritis:a 3 year follow-up on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol.2000,27, 623-9.

6 **Breedveld FC, Han C, Bala M et al.** Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Ann Rheum Dis. 2005;64:52-55.

6a **Van Der kooij et al.** Ann Rheum Disease. 2009 68 914-21. Treating early, especially treating to a defined target is much more likely to achieve remission than prior approaches.

7 **Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J, Whitmore JB.** Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. J Rheumatol. 2004;31:1532-1537.

7a **B Haraovi H El-Gabalawy M Khareshi.** Is the Canadian Health care system neglecting a significant proportion of the Rheumatoid Arthritis population. J Rheumatoid 2009 36 2841-2.

8 **Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN.** The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006;33:2398-2408.

9 **SINGH,JH; Christensen R, WELLS GA' et al.** A network metaanalysis of randomized controlled trials of biologics for rheumatoid arthritis: a Chochrane review CMAJ. 2009, 181, 787-796.

10 **Nixon R, Bansback N, Brennan A.** The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007;46:1140-1147.

11 **Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH.** Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003;62 Suppl 2:ii13-6.:ii13-ii16.

12 **Venkateshan SP, Sidhu S, Malhotra S, Pandhi P.** Efficacy of biologicals in the treatment of rheumatoid arthritis. a meta-analysis. Pharmacology. 2009;83:1-9.

13 **Saag KG, Teng GG, Patkar NM et al.** American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59:762-784.

14 **Bathon JM, Martin RW, Fleischmann RM et al.** A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343:1586-1593.

15 **van der HD, 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;54:1063-1074.

16 **Genovese MC, Bathon JM, Fleischmann RM et al.** Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005;32:1232-1242.

17 **St Clair EW, Van Der Heijde DM, Smolen JS et al.** Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50:3432-3443.

8 **Breedveld FC, Weisman MH, Kavanaugh AF et al.** The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.

9 **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;65:1478-1483.

20 **Weinblatt ME, Kremer JM, Bankhurst AD et al.** A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253-259.

21 **Klareskog L, van der HD, de Jager JP et al.** Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363:675-681.

22 **Maini R, St Clair EW, Breedveld F et al.** Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932-1939.

23 **van de Putte LB, Rau R, Breedveld FC et al.** Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003;62:1168-1177.

24 **Weinblatt ME, Keystone EC, Furst DE et al.** Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48:35-45.

25 **Keystone EC, Kavanaugh AF, Sharp JT et al.** Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400-1411.

26 **Kay J, Matteson EL, Dasgupta B et al.** Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58:964-975.

27 **Keystone E, Heijde D, Mason D, Jr. et al.** Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58:3319-3329.

28 **Edwards JC, Szczepanski L, Szechinski J et al.** Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350:2572-2581.

29 **Lipsky PE, Van Der Heijde DM, St Clair EW et al.** Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343:1594-1602.

30 **Genovese MC, McKay JD, Nasonov EL et al.** Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58:2968-2980.

31 **Furst DE, Schiff MH, Fleischmann RM et al.** Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003;30:2563-2571.

32 **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;144:865-876.

33 **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;52:2263-2271.

34 **Genant HK, Peterfy CG, Westhovens R et al.** Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. Ann Rheum Dis. 2008;67:1084-1089.

35 **Emery P, Keystone E, Tony HP et al.** IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67:1516-1523.

36 **Cohen SB, Emery P, Greenwald MW et al.** Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793-2806.

37 **Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG.** Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis. 2006;65:753-759.

38 **Genovese MC, Becker JC, Schiff M et al.** Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353:1114-1123.

39 **Smolen JS, Kay J, Doyle MK et al.** Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009.

40 **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;67:1096-1103.

41 **Smolen JS, Beaulieu A, Rubbert-Roth A et al.** Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371:987-997.

42 **Nishimoto N, Hashimoto J, Miyasaka N et al.** Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162-1167.

43 **Keystone E, Emery P, Peterfy CG et al.** Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis. 2009;68:216-221.

44 **Lisbona MP, Maymo J, Perich J, Almirall M, Perez-Garcia C, Carbonell J.** Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. J Rheumatol. 2008;35:394-397.

45 **Quinn MA, Conaghan PG, O'Connor PJ et al.** Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:27-35.

46 **Breedveld FC, Emery P, Keystone E et al.** Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004;63:149-155.

47 **Strand V, Balbir-Gurman A, Pavelka K et al.** Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology (Oxford). 2006;45:1505-1513.

48 **Westhaven R; Robles M, Xincenes A C, et al.** Clinical Efficacy and safety of abatcept in melholrexate naive patients with early Rheumatoid Arthritis and poor prognostic factors. Anne Rheum. Dis 2009. 68, 1870-1877

49 **Kremer JM, Genant HK, Moreland LW et al.** Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008;58:953-963.

50 **Westhovens R, Kremer JM, Moreland LW et al.** Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. J Rheumatol. 2009;36:736-742.

51 **Genovese MC, Schiff M, Luggen M et al.** Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008;67:547-554.

52 **Keystone E, Burmester GR, Furie R et al.** Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59:785-793.

53 **Furst DE, Gaylis N, Bray V et al.** Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. Ann Rheum Dis. 2007;66:893-899.

54 **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;66:228-234.

55 **Moreland LW, Weinblatt ME, Keystone EC et al.** Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol. 2006;33:854-861.

56 **van der HD, Burmester G, Melo-Gomes J et al.** The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis. 2008;67:182-188.

57 **Westhovens R, Yocum D, Han J et al.** The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006;54:1075-1086.

58 **Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V.** Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275-2285.

59 **Genovese MC, Cohen S, Moreland L et al.** Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004;50:1412-1419.

60 **van der HD, Klareskog L, Landewe R et al.** Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56:3928-3939.

61 **Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al.** Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52:3381-3390.

62 **Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA.** Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006;24:S-82.

63 **Smolen JS, Van Der Heijde DM, St Clair EW et al.** Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum. 2006;54:702-710.

64 **Taylor PC, Steuer A, Gruber J et al.** Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis Rheum. 2006;54:47-53.

65 **Luqmani R, Hennell S, Estrach C et al.** British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). 2009;48:436-439.

66 **Scott DL, Steer S.** NICE guidelines on anti-tumor necrosis factor therapy for RA. Nat Clin Pract Rheumatol. 2009;5:16-17.

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