

A REVIEW OF EFFECTIVENESS AND SAFETY OF SELECTED BIOLOGICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Authors: Stephen Mwaura Kariuki^{2,3}, Kemoi E.K^{3,4}, Stanslaus Kiilu Musyoki¹

1; School of Health Sciences, Kisii University, P.O Box 408-40200, Kisii, Kenya

2; School of Health Sciences, Mount Kenya University, P.O BOX 2591-30100, Eldoret, Kenya

3; Institute of Tropical Medicine and Infectious Disease, Jomo Kenyatta University of Agriculture and Technology (J.K.U.A.T) P.O. Box 62000, 00200 Nairobi, Kenya.

4; School of Science and Technology, University of Kabianga, P.O Box 2030-20200, Kericho Kenya.

E-mail addresses for authors: SMK (stemwakan@yahoo.com/skariuki@mku.ac.ke); E.K (kemoiedson@gmail.com) and SKM (stanstylo@gmail.com);

*Corresponding author: Email: stemwakan@yahoo.com/skariuki@mku.ac.ke, Mobile phone: +254705426993

Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disease that causes disability to patients in the long run. The bone and cartilage degradation are driven by pro-inflammatory cytokines like tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) among others. The traditional treatment for RA is disease modifying anti-rheumatic drugs (DMARDs) despite the serious adverse effects. In the last past few years biologics have been added to DMARDs or replaced them altogether in the treatment of RA. There is however, growing concern on the effectiveness and safety of these biologics.

Aim: This article reviewed the use of Rituximab, Adalimumab, and Golimumab, as well as dnaJP1 peptide and Folate-targeted immunotherapy data to assess their effectiveness and safety in the treatment of RA.

Methods: Data from clinical trials and other animal model experiments published in peer-reviewed journal articles were reviewed to determine the effectiveness and safety levels of these biologics as used in the treatment of rheumatoid arthritis.

Results: We found that combination therapy of biologics and DMARDs has proven effective in the treatment of RA especially where the latter have failed to reduce disease activity in patients. Rituximab has been found effective where monotherapy treatment with DMARDs and anti-TNFs have failed.

Conclusion: All biologics are generally effective and safe for use in the treatment of RA with minimal side effects being reported.

KEY WORDS: Rheumatoid arthritis, Biologics, DMARDs, Monoclonal antibody, TNF, Safety

Introduction

Traditionally, the treatment and management of Rheumatoid arthritis (RA) has relied on the disease modifying anti-rheumatic drugs (DMARDs). Rheumatoid arthritis is an autoimmune disease that affects joints and can lead to disability. While DMARDs have performed relatively well in the management of this disease through targeting the main inflammatory pathways (Keyser, 2011), there are a number of serious side effects that have been associated with the use of DMARDs. Consequently, scientists have, in the recent past researched and introduced the use of biologics as an alternative in the treatment and management of rheumatoid arthritis (RA). Most of these biologics are monoclonal antibodies raised in animal models against cytokines and other biological players in the pathogenesis of RA. Examples of biologics currently in the market following approval of their use by the US Food and Drugs Administration Agency (FDA) are: Anti-TNF- α e.g. infliximab which is a chimeric antibody, etanercept a recombinant TNF receptor (p75) dimerized on Ig frame, adalimumab a recombinant human IgG monoclonal antibody, golimumab a human monoclonal antibody, and certolizumab pegol a pegylated Fab' fragment from humanized monoclonal antibody (Thalayasingam & Isaacs, 2011; van Vollenhoven, 2009). Other agents already in use in the treatment of RA are tocilizumab an IL-6 receptor inhibitor chimeric monoclonal antibody, rituximab a B-cell directed mAb (Ma & Xu, 2012) and abatacept which blocks T cell activation CD28-CD80/86 pathway (Buch, Vital, & Emery, 2008). These biologics are administered to RA patients either as monotherapy or in combination with the regularly used DMARDs for example methotrexate (MTX), depending on prior disease

treatment outcomes. Etanercept was the first anti-TNF agent to be approved by US Food and Drugs Administration Agency (FDA) for use in the treatment of rheumatoid arthritis (Haraoui & Bykerk, 2007) about 15 years ago.

Although the use of biologics is generally considered safe, some safety concerns have been raised including possible reactivation of latent tuberculosis, hepatitis B and C among others infections (Keyser, 2011; Rubbert-Roth, 2012). Thalayasingam & Isaacs, (2011) states that there is a small increase in opportunistic infections risk in RA patients being treated with anti-TNFs but the risk of cancer and cardiovascular development is low. A publication by (Chen, Chang, Wang, & Wu, 2011) also found the risk of cancer development in RA patients using anti-TNF biologics to be significantly lower relative to the exclusive use of DMARDs among RA patients.

This article seeks to review published data in a number of peer-reviewed publications, to determine the effectiveness and safety of biologics in the treatment and management of RA as the alternative method of treatment. The focus of this review is the efficacy and safety of Rituximab, Adalimumab, and Golimumab in the treatment of rheumatoid arthritis. The use of dnaJP1 peptide and Folate –targeted immunotherapy in the treatment of rheumatoid arthritis will also be reviewed.

Review

Immune-modulating Monoclonal antibodies, Anti-Pro-inflammatory cytokine antibodies and antagonist

The debilitating pain and the crippling cartilage and bone degradation in RA patients is driven by inflammatory reactions. The pro-inflammatory cytokines produced by various

immune cells particularly the Th1 cells is the force behind these reactions (Chatzidionysiou, 2012).

a) Rituximab

Rituximab which is a chimeric monoclonal antibody raised against CD20 antigen on B cells has been found to be a much more effective treatment in RA patients than TNF- α inhibitor - TNFi (Emery et al., 2014). The anti-CD20 exerts its action by depleting the CD20⁺ B cells in RA patients (Paul Emery, 2012). An efficacy randomized trial by (Emery et al., 2006) had shown that 2500-mg or 2 1,000-mg infusions of rituximab achieved a 20% improvement in disease activity relative to placebo ($p < 0.0001$) on RA patients when assessed at the 24th week. This assessment was done based on American College of Rheumatology criteria 20 (ACR20). A study by (Cohen et al., 2006a) found a significant difference ($p < 0.0001$) in the treatment of RA patients with a treatment course with two infusions of 1000mg rituximab each compared to RA patients on placebo at 24 weeks. Assessment was based ACR20 where the improvement results for rituximab patients compared to placebo at 51% versus 18% respectively.

In another study, (Emery et al., 2014) demonstrated that rituximab when administered to RA sero-positive patients who had shown inadequate positive response to TNF- α inhibitors at the baseline shows significant improvements. A follow-up of two groups of patients, one who had been treated with alternative TNF- α inhibitor and the other group with rituximab for 6 months after inefficient response by the first TNF inhibitor treatment, showed significant improvement (Based on Disease Activity Scores (DAS28)) in rituximab-treated RA patients relative to the alternative TNFi-treated patients ($p = 0.011$). These results suggest that rituximab is a better alternative treatment to RA patients where TNFi has failed.

b) Adalimumab

Adalimumab was the first fully humanised anti-TNF monoclonal antibody to be used in the treatment of RA patients particularly where regular DMARDs have proven ineffective and poorly tolerated (Mease, 2007). A double blind, placebo controlled, phase III clinical trial conducted on RA patients by (van de Putte et al., 2004) showed a 35.8% and 39.3% ACR20 improvement when 20mg of adalimumab was administered one other week compared to weekly administration respectively. When the same researchers administered 40mg one other week and weekly to RA patients the results were better at 46.0% and 53.4%, respectively using the same American criteria ACR20. When these results were compared with those of a placebo (19.1%), the difference on efficacy was significant at $p < 0.01$ (See table 1). The pattern of these results was replicated when assessed at secondary end points ACR50 and ACR70. This data suggests that adalimumab is more efficacious at a higher dose and at a higher frequency of administration. The adverse results were minimal and comparable between patients treated with adalimumab and those treated with the placebo.

In another study (Bennett et al., 2005) treated 70 patients of RA with adalimumab and found mean of 2.1 (6.3–4.2; $P < 0.001$) decrease in Disease Activity Score 28 (DAS28). They also found a mean decrease of 0.34 (2.07–1.73; $P < 0.001$) in Health Assessment Questionnaire (HAQ) score (See table 1). In that study 23% of the participants stopped treatment because of either treatment failure (16%) or undesirable effects (7%). Out the 70 patients, 26 patients had tried other biologics and failed. Of the 26 patients 65% responded well to adalimumab. This data suggests that adalimumab is effective and relatively safe in the treatment of RA particularly where other biologics and regular DMARDs have failed to show decrease in disease activity.

c) Golimumab

Golimumab is a fully humanised anti-TNF- α antibody used in the treatment of RA (Kay & Rahman, 2009) among other human disease conditions. A clinical trial involving RA patients who have been treated with methotrexate (MTX) but with inadequate response in reduction of disease activity, in a 2 years follow-up study compared golimumab + MTX with placebo + MTX (Keystone et al., 2013). They found that there was a 55.6% ACR20 response at week 14 of the trial in RA patients treated with golimumab (50mg) + MTX compared with 33.1% ACR20 response in patients treated with placebo + MTX. This difference was statistically significant at $P < 0.001$ (see table 1). In the same study, at 104 week 90% of RA patients treated with golimumab + MTX maintained an ACR20 response. The incidence of infections following treatment with golimumab was minimal. This means that golimumab does not only improve the symptoms of disease activity in RA patients but can maintain the improvement in long term safely.

Another study compared the decrease in inflammatory serum markers in RA patients treated with golimumab 100mg administered subcutaneously and patients treated golimumab 2mg/1kg administered intravenously (Doyle et al., 2013). These authors found that there was a decrease in CRP, SAA, MMP-3, TNFR2, haptoglobin, IL-6, ferritin and hepcidin. There was a decrease in mean urine levels of hepcidin within the first week through to week 8, in both subcutaneous administration and intravenous administration but this decrease was maintained up to week 24 only in the later case. This data may suggest that golimumab should best be administered intravenous to maintain its efficacy for longer in the treatment of RA.

Antigenic Peptides Approach

a) dnaJP1 peptide

Research has demonstrated that oral administration of dnaJP1 peptide in RA patients deviates the T cell proliferation to that of regulatory T cells generation that produce IL-4 and IL-10 and suppresses the generation of IFN- γ , IL-2 and TNF- α which are all pro-inflammatory cytokines (Prakken et al., 2004). In their study, (Prakken et al., 2004) recruited patients in early (<5 years) stages of RA, with at least six joints swollen and tender, based on the American College of Rheumatology (ACR) criteria for RA. These patients were treated for a duration of 6 months. Mucosal therapy with dnaJP1 peptide was found to be an effective, beneficial and safe biologic in the treatment of RA patients (Table 1). These findings suggest that dnaJPI peptide can be used as a protective immune modulation therapy in RA patients at early stages of the disease.

b) Folate –targeted immunotherapy

Activated macrophages have been found to over-express receptors for folic acid in RA mice models (Piscaer et al., 2011). Activated macrophages produce pro-inflammatory cytokines including the TNF- α (Haraoui & Bykerk, 2007) which is a pleiotropic cytokine that plays a critical role in the pathogenesis of arthritis (Thalayasingam & Isaacs, 2011). This concept of over-expression of receptors for folic acid has been used by scientists in the delivery of radio-active molecules in joints of RA in order to visualize through radiography the level of accumulation of activated macrophages, which correlates with inflammation in these joints. The intensity of inflammation indicates the degree of severity of cartilage and bone degradation (Paulos et al., 2006). That study (Paulos et al., 2006) hence used the same concept to deliver the folate-hapten conjugate in already hapten-immunized (hence with anti-hapten antibodies) rats and demonstrated that the immune cells having receptors for the Fc region of anti-hapten antibodies were able to clear activated macrophages in their sites of accumulation. This was found to significantly reduce cartilage and bone degradation in rats

Journal of Biological Science

limbs (p <0.001) to a level of performance comparable to the commonly used disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, etanercept, anaconda and celecoxib (Paulos et al., 2006). The researchers also reported no toxicity in the major organs of the body e.g. liver, kidney and brain (table 1).

Table 1: Performance of different biologics in treating Rheumatoid Arthritis

S/NO	BIOLOGIC/DRUG	ANIMAL TYPE	ROUTE OF ADMINISTRATION	ACTION INDUCED	BENEFIT TO RA PATIENTS	SAFETY TO RA PATIENTS	AUTHOR
1.	DnaJP1 peptide	Human	Oral (Mucosal Therapy)	-Up regulation of Reg T cells (CD4 ⁺ CD25 ^{Bright}) marked by expression of foxP3 -Induction of IL-4 and IL-10 -Decrease in IFN-γ, IL-2 and TNF-α (p <0.001)	Reduction of RA symptoms including pain, slowing disease progression	No adverse effects reported	(Prakken et al., 2004)
2.	Folate-hapten Conjugates	Rats	Intraperitoneal (Folate-targeted Immunotherapy)	-Elimination of activated macrophages (p <0.001)	Reduction of inflammation and cartilage/bone degradation in mice limbs	No toxicity on major organs: Liver, kidney and brain	(Paulos et al., 2006)
3.	Rituximab (Anti-CD20) & TNFi	Human	Intravenous	Depletion of CD20+ B cells in RA patients by rituximab TNFi blocks the pro-	Reduction of disease activity by Rituximab more than TNFi (p=0.011)	Similar adverse effects in both - Minimal	(Emery et al., 2014)

Journal of Biological Science

				inflammatory action of TNF			
4.	2 500-mg or 2 1,000-mg infusions of rituximab	Human	Intravenous	Depletion of CD20+ B cells in RA patients by rituximab	Reduction of disease activity by Rituximab more than TNFi (p<0.0001)	Relatively safe and tolerable	(Emery et al., 2006)
5.	1000mg of rituximab	Human, previously treated with	Intravenous	Depletion of CD20+ B cells in RA patients by rituximab	Improvement on disease activity ACR20 (51% versus 18%),	Adverse mild-to - moderate severity; 5.2% out of 100 infections	(Cohen et al., 2006b)
6.	20mg & 40mg Adalimumab	Human	Intravenous	Anti-TNF activity	Improvement on disease activity at ACR20: 20 mg – 35.8% (One other week) & 39.3% (weekly). 40mg – 46.0% (one other week) & 53.4% (weekly) (P<0.01)	Minimal adverse effects comparable to placebo	(van de Putte et al., 2004)
7.	Adalimumab	Human	Intravenous	Anti-TNF activity	2.1 (6.3–4.2; P<0.001) decrease in Disease Activity Score 28 (DAS28)	7% of 70 patients with side effects	(Bennett et al., 2005)

Journal of Biological Science

				0.34 (2.07–1.73; P<0.001) in Health Assessment Questionnaire (HAQ) score.		
8.	Golimumab and/or Methotrexate (MTX)	Subcutaneous	TNF-α activity neutralization	Reduction of Disease activity: 55.6% ACR20 response in Golimumab + MTX 33.1% ACR20 response in placebo + MTX	Minimal adverse effects	(Keystone et al., 2013)

CONCLUSION

Combination therapy of biologics and DMARDs is more effective in the treatment of rheumatoid arthritis than monotherapy of either of the two. Rituximab a monoclonal antibody targeting to delete activated B cells in RA patients has particularly been found effective where monotherapy treatment with DMARDs and anti-TNFs have failed. All biologics are generally safe for use in the treatment of RA with minimal side effects being reported.

References

- Bennett, a N., Peterson, P., Zain, a, Grumley, J., Panayi, G., & Kirkham, B. (2005).
 Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. *Rheumatology (Oxford, England)*, *44*(8), 1026–31. doi:10.1093/rheumatology/keh673
- Bennett, A. N., Peterson, P., Zain, A., Grumley, J., Panayi, G., & Kirkham, B. (2005).
 Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. *Rheumatology*, *44*, 1026–1031. doi:10.1093/rheumatology/keh673
- Buch, M. H., Vital, E. M., & Emery, P. (2008). Abatacept in the treatment of rheumatoid arthritis. *Arthritis Research & Therapy*, *10 Suppl 1*, S5. doi:10.1186/ar2416
- Chatzidionysiou, K. (2012). Biologic Treatment in Rheumatoid Arthritis.
- Chen, Y.-J., Chang, Y.-T., Wang, C.-B., & Wu, C.-Y. (2011). The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. *Arthritis and Rheumatism*, *63*, 352–358. doi:10.1002/art.30134
- Cohen, S. B., Emery, P., Greenwald, M. W., Dougados, M., Furie, R. a, Genovese, M. C., ... Totoritis, M. C. (2006a). 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 and Rheumatism*, *54*(9), 2793–806. doi:10.1002/art.22025
- Cohen, S. B., Emery, P., Greenwald, M. W., Dougados, M., Furie, R. A., Genovese, M. C., ... Totoritis, M. C. (2006b). 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 and Rheumatism, 54, 2793–2806. doi:10.1002/art.22025

Doyle, M. K., Rahman, M. U., Frederick, B., Birbara, C. a, de Vries, D., Toedter, G., ...

Furst, D. E. (2013). Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial. *Rheumatology (Oxford, England)*, 52(7), 1214–9.

doi:10.1093/rheumatology/kes381

Emery, P. (2012). Optimizing outcomes in patients with rheumatoid arthritis and an inadequate response to anti-TNF treatment. *Rheumatology (Oxford, England)*, 51 Suppl 5, v22–30. doi:10.1093/rheumatology/kes115

Emery, P., Fleischmann, R., Filipowicz-Sosnowska, A., Schechtman, J., Szczepanski, L., Kavanaugh, A., ... Shaw, T. M. (2006). The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis and Rheumatism*, 54(5), 1390–400. doi:10.1002/art.21778

Emery, P., Gottenberg, J. E., Rubbert-Roth, a, Sarzi-Puttini, P., Choquette, D., Martínez Taboada, V. M., ... Finckh, a. (2014). Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Annals of the Rheumatic Diseases*. doi:10.1136/annrheumdis-2013-203993

Haraoui, B., & Bykerk, V. (2007). Etanercept in the treatment of rheumatoid arthritis.

Therapeutics and Clinical Risk Management, 3(1), 99–105.

doi:10.2147/tcrm.2007.3.1.99

Kay, J., & Rahman, M. U. (2009). Golimumab : A novel human anti-TNF- α monoclonal

antibody for the treatment of rheumatoid arthritis , ankylosing spondylitis , and psoriatic arthritis, 159–170.

Keyser, F. De. (2011). Choice of Biologic Therapy for Patients with Rheumatoid Arthritis:

The Infection Perspective. *Current Rheumatology Reviews*, 7(1), 77–87.

doi:10.2174/157339711794474620

Keystone, E. C., Genovese, M. C., Hall, S., Miranda, P. C., Bae, S.-C., Palmer, W., ... Hsia,

E. C. (2013). Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension.

The Journal of Rheumatology, 40(7), 1097–103. doi:10.3899/jrheum.120584

Ma, X., & Xu, S. (2012). TNF Inhibitor Therapy for Rheumatoid Arthritis, *I*(2), 1–7.

doi:10.4172/scientificreports.15

Mease, P. J. (2007). Adalimumab in the treatment of arthritis. *Therapeutics and Clinical Risk*

Management, 3(1), 133–148. doi:10.2147/tcrm.2007.3.1.133

Paulos, C. M., Varghese, B., Widmer, W. R., Breur, G. J., Vlashi, E., & Low, P. S. (2006).

Folate-targeted immunotherapy effectively treats established adjuvant and collagen-induced arthritis. *Arthritis Research & Therapy*, 8(3), R77. doi:10.1186/ar1944

Piscaer, T. M., Müller, C., Mindt, T. L., Lubberts, E., Verhaar, J. a N., Krenning, E. P., ...

Weinans, H. (2011). Imaging of activated macrophages in experimental osteoarthritis

using folate-targeted animal single-photon-emission computed tomography/computed tomography. *Arthritis and Rheumatism*, 63(7), 1898–907. doi:10.1002/art.30363

Prakken, B. J., Samodal, R., Le, T. D., Giannoni, F., Yung, G. P., Scavulli, J., ... Albani, S. (2004). Epitope-specific immunotherapy induces immune deviation of proinflammatory T cells in rheumatoid arthritis. *Proceedings of the National Academy of Sciences of the United States of America*, 101(12), 4228–33. doi:10.1073/pnas.0400061101

Rubbert-Roth, A. (2012). Assessing the safety of biologic agents in patients with rheumatoid arthritis. *Rheumatology (Oxford, England)*, 51 Suppl 5(March), v38–47. doi:10.1093/rheumatology/kes114

Thalayasingam, N., & Isaacs, J. D. (2011). Anti-TNF therapy. *Best Practice & Research. Clinical Rheumatology*, 25(4), 549–67. doi:10.1016/j.berh.2011.10.004

Van de Putte, L. B. a, Atkins, C., Malaise, M., Sany, J., Russell, a S., van Riel, P. L. C. M., ... Kupper, H. (2004). Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Annals of the Rheumatic Diseases*, 63(5), 508–16. doi:10.1136/ard.2003.013052

Van Vollenhoven, R. F. (2009). Treatment of rheumatoid arthritis: state of the art 2009. *Nature Reviews. Rheumatology*, 5(10), 531–41. doi:10.1038/nrrheum.2009.182