Citation: Naqvi, S. F. U. H., & Shehnaz, G. (2020). A Deep Insight on Rheumatoid Arthritis, Indexes (Disease Activity Score 28 (DAS28), ESR, CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Global Health) and Correlation with the Level of Disease Activity. *Global Immunological & Infectious Diseases Review, V*(I), 1-8. https://doi.org/10.31703/giidr.2020(V-I).01

ISSN (Print): 2788-4961 | **ISSN (Online):** 2788-418X | **URL:** http://dx.doi.org/10.31703/giidr.2020(V-I).01

Pages: 1 – 8 | **DOI:** 10.31703/giidr.2020(V-I).01 | **Vol.** V**, No.** I (2020)

A Deep Insight on Rheumatoid Arthritis, Indexes (Disease Activity Score 28 (DAS28), ESR, CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Global Health) and Correlation with the Level of Disease Activity

Syed Faaez Ul Hassan Naqvi [*] | Gul Shehnaz [†]

Abstract *Rheumatoid arthritis as one of the autoimmune diseases is more prevalent now than ever before. Being more common in women than men, RA has been focused by researchers to invent a therapeutic agent for effective clinical response. Various Diagnostic biomarkers are being used for early diagnosis of RA depending upon their selectivity and specificity. Certain indexes for RA disease activity evaluation are used for assessment of disease on a continuous scale. Disease activity Score combined with laboratory data result and imaging technologies makes the decision of treatment strategies easier than before. Traditionally, TNFi are the most used agents since a decade and first choice of treatment by clinicians, however, combination therapy with DMARD is used in inadequate responders. Despite all the advancements in treatment of RA and proved remission possibility using latest biological agents, studies are needed to ensure quick clinical outcomes and remission probability in larger fraction of people.*

Key Words: Rheumatoid Arthritis, TNFi, DAS28, Anti – CCP, IL – 17A

Introduction

Rheumatoid arthritis (RA) is a prototype chronic autoimmune disease, occurs most commonly in middle aged women, and for most part affects synovial tissues. Occurring majorly in 3rd to 5th decade of life, RA is caused may be due to genetic as well as environmental factors. RA is identified in 80% of patients (Almaliotis et al., 2016) who have positive RA factor, but also Anti CCPs has great importance for the diagnosis of disease and must principally be diagnosed in early stages of disease development. A broad spectrum of autoantibodies is being used in clinical research to assess the development of RA in patients as serum diagnostic biomarkers including the two of them mentioned earlier. Diagnosis of RA is difficult however American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) has provided a criterion to identify RA patients with relatively great accuracy. ACR 1987 criteria was more specific as compared to ACR/EULAR 2010 Criteria (Ebel & O'Dell, 2021) but less sensitive than the later. Considering symptoms, wholly, may lead to false positive diagnosis of RA, therefore 2010 ACR/EULAR criteria include some laboratory data e.g., CRP, ESR, Rheumatoid factor and ACCPs.

RA is believed to be systemic autoimmune disease and signs, and symptoms begin from the eye like other autoimmune diseases (Almaliotis et al., 2016). Moreover, RA may cause dysfunction of small joints of hands, and rarely in feet, shoulders, and elbows. RA may present certain skin abnormalities as symptoms along with some of ocular indications (Almaliotis et al., 2016)

Prevalence of RA is more and referred to global burden of disease 2010 which states that prevalence

[*] Undergraduate Student, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
[†] Chairperson, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
Email: gshahnaz@qau.edu.pk *(Corresponding Author)*

of RA is 0.24% with 4:2 in women and men and 5-50 out of each lac of population is reported with RA every year (Ananthathandavan & Vijayakumar, 2020), hence, clinical Treatment goal of RA is to achieve "No signs & symptoms of inflammation". RA patients may have compromised Quality of life (QOL), limited Activities of Daily Living (ADL) and functional disability along with pain in joints and systemic inflammation. However, RA progresses in some of the patients very quickly and the goal of treatment is to retard the progression of the disease. If left unattended, may lead to multiple joint dysfunctions, comorbidities, and ultimately death.

The study in this article is concentrated at link between various indexes of rheumatoid arthritis and the condition of patient is under which criteria (remission, mild, severe, very severe), and whether the treatment using any biologic is needful, according to American College (ACR) and European League Against Rheumatism (EULAR) 2010 criteria.

Literature Search

The detailed investigation about clinical experience of authors and literature search was done to understand and collect maximum data and information about the rheumatoid arthritis and indexes along with criteria to evaluate the disease activity. The relevant academia was searched using different relatable terms. Such terms included "RA" along with treatment biologic ("TNFi"), indexes for evaluation ("DAS28", "SDAI", "CDAI"), Diagnostic immunological markers ("RA factor", "Anti-CCPs", "CRP", "ESR"). "Modern treatment strategies" was also searched in literature with close relationship to knowledge rich journals of "American College of Rheumatology (ACR)". Evaluation criteria and detailed study was conducted about "American Rheumatism Association (ARA)", currently "ACR", and "ACR/EULAR 2010" was understood for evaluation of disease activity of patients. Reference lists of some relevant articles and editorials were also acknowledged

.

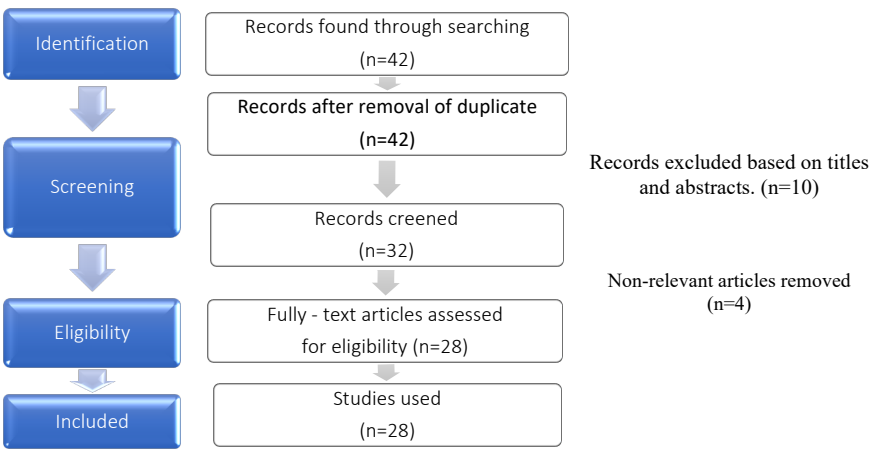

Figure 1: PRISMA Flowchart: RA and evaluation criteria for selection of essential treatment.

Diagnosis and Treatment of RA

According to definition of biomarker by National Institutes of Health's Biomarkers and Surrogate Endpoint Working Group, a biomarker is a feature we can measure and evaluate as indicator of biological process, pathogenesis, and pharmacological response to any treatment. Owing to needs, the standard for being a biomarker is specificity and sensitivity is under research since recent years (Harpreet Kaur, 2012).

The characteristics of an ideal biomarker include 100% sensitivity, specificity and positive predictive value referring to the fraction of people showing positive test and having disease (Harpreet Kaur, 2012).

Some of the biomarkers used for the diagnosis of include:

1- Rheumatoid Factor (RF)
2- Anti-cyclic citrullinated peptide (Anti CCP)

3- Micro RNA (miRNA)
4- Anti-mutated citrullinated Vimentin (anti MCV)
5- Anti-filaggrin antibodies (AFA)
6- Interleukin – 22 (IL – 22)

RF is more established biomarker for RA diagnosis but least specific (less than 50%) owing to its presence in other infectious and autoimmune diseases as well but is 70%-80% sensitive. While Anti CCP is more specific (>95%) to RA and can be used as reliable marker for the positive prediction in the diagnosis of RA(Harpreet Kaur, 2012). Clinical practices and research has indicated the use of Anti CCP, RF in combination with Anti CCP or anti MCV or other biomarkers for effective diagnosis of RA(Harpreet Kaur, 2012).

As far as clinical intervention is concerned, it works best if diagnosis of RA is done in very early stages. Therefore, recent studies have been focused on such biomarker which can access the early-stage activity of RA in patients or suspected patients can be evaluated and warned for any future synovitis (Yamasaki et al., 2016). In the recent years, Myeloid related protein (MRP) 8/14 has got attention as an evaluation parameter for the synovitis activity in RA. Studies have proved the co-relation between MRP 8/14 with the disease activity of RA (Yamasaki et al., 2016).

Disease activity of RA, on which this study is focused, can be evaluated by various indexes which utilize physical as well as laboratory examination of patients and can help the patients to evaluate themselves, as well clinicians for any therapeutic intervention.

Major targets to be achieved for the treatment of RA is to avoid the pain and inhibition/control of synovitis in joints. While we aim at more reliable evaluation parameter for assessment of RA disease activity, based on trials, American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and World health organization/International League Against Rheumatism (WHO/ILAR) have devised some core variables which include TJC, SJC, Patient Global Health etc. (Medeiros et al., 2015).

Few other indexes for assessment of RA activity were proposed in clinical practice which measure the disease activity on a continuous scale and categorizes the disease activity using cut-off points as remission, mild, moderate, and high disease activity e.g., Disease Activity Score 28 (DAS28) which utilizes ESR, TJC, SJC, Patient Global Health assessment and ESR. The pioneer DAS, however, makes use of 26 joints to evaluate painful joints and 44 joints to evaluate the swollen ones. DAS28, proposed later and most used till now, uses 28 joints for assessment of pain and swelling and allowed use of either ESR or CRP as inflammatory marker. The calculation if DAS28 is difficult as it uses logarithm and requires a computational tool for calculation(Medeiros et al., 2015).

Table 1. DAS28-CRP assessment (Medeiros et al., 2015; Yamasaki et al., 2016).

Score	Disease Activity Assessment
<2.3	Remission
2.3-3.2	Low
3.3-5.1	Moderate
>5.1	High

Later, some of the more simplified indexes were proposed including Simplified Disease Activity (SDAI) and Clinical Disease Activity Index (CDAI). SDAI is measurement using sum of number of swollen and tender joints, evaluation score of patients by himself on visual analogue scale from 0-10cm (with 0 being "doing very well" and 10 being "doing very poor"), evaluation score of patients by physician on scale of 0-10cm (with 0 being "doing very well" and 10 being "doing very poor") and CRP (mg/dl) (Medeiros et al., 2015).

Table 2. SDAI evaluation (Medeiros et al., 2015; Yamasaki et al., 2016). .

Score	Disease Activity Assessment
<3.3	Remission
3.3-11	Low

11-26	Moderate
>26	High

CDAI is simpler and uses all the scores used for SDAI except CRP(Medeiros et al., 2015).

Among all the above-mentioned disease activity indexes, DAS28 is most validated one while it can use ESR and CRP both. However, use of DAS28 using CRP still requires deeper research study(Medeiros et al., 2015). Visual analogue scale for patients' pain assessment is done by using scale in millimeters and classified as:

Table 3. Pain Assessment (Medeiros et al., 2015; Yamasaki et al., 2016).

Scale	Pain assessment
0-4mm	No pain
5-44mm	Mild
45-74mm	Moderate
75-100mm	Severe
100+mm	Very severe

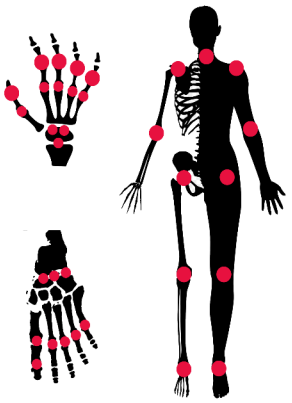

Figure 2: Joint evaluated in Tender Joint Count/Swollen Joint Count used for score calculation of DAS28, SDAI, CDAI in RA.

Apart from the evaluation of disease activity parameters discussed above, ultrasonography and laboratory reports are also performed. However, studies showing MRP8/14 as effective diagnostic marker and evaluation method has proved a ray of hope in the successful diagnosis of RA (Yamasaki et al., 2016).

Evaluation of synovitis activity, performed by using all these parameters, is important for assessment of disease and initiation of any clinical intervention in or changing of therapeutic treatment for RA Patients (Yamasaki et al., 2016).

The first criterion for the assessment of RA disease was established by American Rheumatism Association (ARA). A committee including 5 rheumatologists were given the task of devising a criterion to access the disease activity and relate the progression, incidence, course, manifestations, treatment, and other features of RA. The criteria defined definite RA, probable RA, possible RA. The criteria were used for approximately 3 decades until the new 1987 ARA criteria were proposed given in table 3. American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) proposed a criterion in 2010, and over-ruled the existing 1987 criteria, to know the need of treatment. The new criteria have proved to more sensitive (97%) to detect RA but has less specificity compared to 1987 criteria i.e., 55% versus 76%. The authors evaluated and compared the criterion of both classification systems and found no significant difference among them, also, studies have shown the need of new

criteria for evaluation of RA disease activity and progression which, if history repeats itself, maybe in the next 20 years (Liao & Bykerk, 2011).

The evaluation criteria include a set of parameters given in Table. 4. Unlike 1987 ARA criteria, 2010 ACR/EULAR evaluation is applicable to patients with disease of <6 weeks' duration, also, structural damage is not part of new RA classification criteria (Kay & Upchurch, 2012).

Table 3. 1987 ARA Classification criteria (Kay & Upchurch, 2012).

1987 Classification criteria by ARA
Morning Stiffness > 1 hr
Arthritis of 3 joint areas
Arthritis of hands
Symmetric arthritis
Rheumatoid nodules
Serum RF
Typical radiographic changes
Time duration must be greater than 6 weeks

According to 1987 ARA Classification criteria point scores from each domain in table 3. is added and total score of greater than or equal to 4 is required to classify a patient having Rheumatoid Arthritis (Ebel & O'Dell, 2021).

Table 4. 2010 ACR/EULAR Classification criteria (Kay & Upchurch, 2012).

Domain	Category	Point Score
A	Joint involvement	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints with at least 1 small joint	5
B	Serology	
	Neg – RF and ACPA	0
	Low positive RF or ACPA	2
	High positive or high positive RF or ACPA	3
C	Acute phase reactants	
	Normal CRP and normal ESR	0
	Abnormal or Abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	> or equal to 6 weeks	1

According to 2010 ACR/EULAR classification criteria point scores from each domain in table 4. is added and total score of greater than or equal to 6 is required to classify a patient having Rheumatoid Arthritis (Kay & Upchurch, 2012).

All the above parameters for disease diagnosis or evaluation of disease activity ultimately leads to decision making for using effective treatment. Modern treatment strategies now a days makes remission of disease a possible reality.

Physicians initiate the treatment of RA after diagnosis with Tumor Necrosis factor – Inhibitors (TNFi) as first line biologics e.g., adalimumab, golimumab, infliximab, etanercept, abatacept etc. The reason behind this maybe that TNFi was the first biologic to be used for treatment of RA and physicians now have most experience with them as clinically effective therapeutic agents in RA. TNFi, if fail to effectively treat patients, is followed by other biologics or agents with different mechanism of action (Pope & Combe, 2013).

The last decade saw a transition in treatment of RA from simple immunomodulatory agents to more effective biotherapies with a gradual increase in efficacy of agents. However, research studies are focused now on devising strategies to lessen the disease activity and remission as much as possible in significant proportion of patients (Launois et al., 2011). Treatment efficacy of any of the therapeutic agent is accessed and proved to be established according to set criteria of ACR for all the agents showing the fraction of remission caused by it. The fraction is denoted by ACR20, ACR50 or ACR70 with ACR20 being the primary efficacy criterion (Launois et al., 2011).

Recent advancements in last decade have improved our ability to improve the treatment strategies of RA, reducing the signs and symptoms, improvement of Quality of life, reducing joint damage, synovitis, and functional loss. Studies have been performed to access the long-term use of TNFi and other biologics in terms of safety profiles and efficacy over prolonged use. However, concerns were expressed about serious adverse effects and close monitoring of patients with high RA activity is necessary (van Vollenhoven et al., 2010). Studies have shown the use of TNFi as safe for long-term exposure; however, the risk of infection or malignancy is still rising the questions and require increased monitoring in long-term treatment (E. C. Keystone, 2011).

Inadequate response to any of the initial treatment compels clinicians to change the treatment agents. However, TNFi being the first line of treatment whether used as monotherapy or combined with traditional Disease modifying anti rheumatic drugs (DMARD) such as methotrexate (MTX) (E. C. Keystone, 2011).

The traditional treatment agents include DMARDs to retard disease progression and Analgesics to improve symptoms, however, invention of newer TNFi has caused greater burden on the treatment cost of RA although remaining most effective treatment. The costs and budget considerations are impossible to ignore as far as the treatment of RA is considered by clinicians. Because of this, clinicians try to consider low-cost agents first, which may or may not effectively treat the patient, ultimately declined patient health forcing them to use costly treatment agents. This failure to quickly achieve remission or treatment may lead to declined symptom control and irreversible synovitis and joint damage in RA patients. While researchers have been trying to devise cost effective treatment strategies, studies have shown the step up or step-down treatment of DMARD is most cost-effective strategy (Tosh, Wailoo, Scott, & Deighton, 2011).

In some countries, the decision to continue the therapy is solely based on DAS and EULAR criteria of RA disease where clinicians and rheumatologists must follow up the treatment, follow their patients and make treatment decisions accordingly. Another important question to address is that those people with low DAS must not be treated intensively as this may lead to severe complications other than RA itself. Therefore, this is what clinicians and rheumatologists must do in clinical practice. Other patient characteristics must be considered, as cost considerations directly or indirectly affect the daily practice of RA patients, for modelling of treatment strategies.

With the advent of new literature, it is considered feasible to take effective treatment and cost effectiveness parallel with each other, where DAS evaluation will drive clinicians to rethink and remodulate the treatment used for the patients.

In the recent years where RA is becoming more prevalent, treatment strategy must be developed to ensure quick control of disease activity. All above discussed treatment strategies including monotherapy as well as combination therapy has proved effective treatment in long-term exposure for RA patients. The studies have shown the importance of sustained and controlled treatment for preventing the joint damage as well as functional loss in RA patients. In this regard, TNFi and DMARD have proved beneficial in lessening the signs and symptoms and health related quality of life, while inhibition of structural damage has been a priority in treatment of RA (E. Keystone et al., 2011).

Apart from short-term clinical efficacy, studies have supported the timing of response in patients with RA as important predicting measure as people who show quick response to therapy are most likely to sustain and show outcomes from that therapy in long-term (E. Keystone et al., 2011).

Unmet Needs in the Treatment

The advancement in the clinical studies have established some basic treatment guidelines for the effective clinical outcomes and improved quality of life with patients undergoing little joint damage and functional loss caused by synovitis in RA, and also it has significantly reduced permanent disabilities and

extraarticular complications over the past few years such that clinically remission is considered as practically possible reality in RA patients now. While the advancements in the treatment of RA are discussed, there are still some of the unmet needs and unattended domains in the investigational approaches for effective clinically therapeutic agents. In the recent randomized clinical trials, the use of TNFi in combination therapy with MTX has proved effective than TNFi or MTX alone in patients MTX has proved less effective (Pope & Combe, 2013)..

Some of the biologics which are being used in the clinical treatment of RA include abatacept, rituximab, tocilizumab, baricitinib, and fostamatinib with each having different mechanism of action. However, these agents present ceiling effect with ACR50 and ACR70 in limited fraction of patients (Pope & Combe, 2013).

Patients who lose their response to TNFi may or may not give effective response to other biologics therefore, we can utilize the change in therapy within the same class. Studies have shown that within TNFi clinicians can make use of second choice or even third choice of biologics within the same class for improved response in inadequate responders (Pope & Combe, 2013).

Although, studies have given a review about using second or third line of therapy for patients having RA but unfortunately, it has given no clue about which therapy could be used next (Pope & Combe, 2013). Also, it has put little light over the question of which patient should be treated by which of the drug as first line treatment whether monotherapy or combination therapy is utilized (Ebel & O'Dell, 2021).

There are also some unattended domains in identification of specific biomarkers or indicators which can give clue about best possible treatment for individual patients. Moreover, further research is required to maintain the luck of patients who, fortunately, get remission but unable to titrate the DMARD therapy ultimately leading to unavoidable complications or drug overuse. Apart from this, patient compliance to medications on regular basis remains significant question to be answered (Ebel & O'Dell, 2021).

Some of the researchers have tried to answer these questions by using knowledge about clinical outcomes and therapeutic agents. Studies suppose that clinical characteristics and outcomes of the treatment are the decisive factors in the continuation or change of therapy. Clinically identifiable characteristics or biomarkers in individual patients should be used while deciding the fate of any therapy on follow up by clinicians.(Pope & Combe, 2013).

Based on the disease activity DAS28, we can evaluate the activity of any therapeutic agent. However, this is not unexpected fact that higher disease activity offers better ACR50 or ACR70 response. While less disease activity may give a clue to get easy remission by utilizing rational therapeutic approach (Pope & Combe, 2013).

Various biomarkers like RF, Anti CCP and other protein markers have been evaluated for the assessment of TNFi response in individual patients but unfortunately, no clue giving the co-relation between the disease activity and TNFi response rate has been found yet. However, as far as recent advancements are concerned, it can be expected in near future for establishment of a factor or biomarker or any clinical characteristic which can be evaluated by clinicians to identify and decide the fate of therapy being used in patients (Pope & Combe, 2013).

TNFi are being used since a decade and was developed at the time when RA was found to be Th1-mediated disease leading to the production of inflammatory cytokines mainly TNF-alpha, IL - 1beta, IL – 6. However, novel approaches are being applied for the identification of more specific biomarkers or mediators that can be inhibited. One of them that is under research study is interleukin – 17A which works differently from the role of Th1 pathway and its cytokines but thought to be important role player in RA based on both clinical and pre-clinical data and can be expected to be a viable therapeutic target in next few years (Pope & Combe, 2013).

References

Almaliotis, D., Zakalka, M., Gerofotis, A., Chatzicharalampous, K., Efstathiou, M., Daniilidis, M., & Karampatakis, V. (2016). Ocular Manifestations in Rheumatoid Arthritis. *Open Journal of Ophthalmology, 06*, 170-175. doi:10.4236/ojoph.2016.63024

Ananthathandavan, P., & Vijayakumar, T. (2020). Safety and Efficacy of newer biologics DMARDs in the management of Rheumatoid Arthritis: A Systematic Review. *Osteoarthritis and Cartilage Open, 2*. doi:10.1016/j.ocarto.2020.100116

Ebel, A., & O'Dell, J. (2021). Clinical Features, Diagnosis, and Treatment of Rheumatoid Arthritis. *Physician Assistant Clinics, 6*, 41-60. doi:10.1016/j.cpha.2020.08.004

Harpreet Kaur, J. S. (2012). Diagnostic Biomarkers in Rheumatoid arthritis – An update. *Der pharmacia sinica*, 408-412.

Kay, J., & Upchurch, K. (2012). ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology, 51*, vi5-vi9. doi:10.1093/rheumatology/kes279

Keystone, E., Curtis, J., Fleischmann, R., Furst, D., Khanna, D., Smolen, J., . . . Combe, B. (2011). Rapid Improvement in the Signs and Symptoms of Rheumatoid Arthritis Following Certolizumab Pegol Treatment Predicts Better Longterm Outcomes: Post-hoc Analysis of a Randomized Controlled Trial. *The Journal of rheumatology, 38*, 990-996. doi:10.3899/jrheum.100935

Keystone, E. C. (2011). Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: a review of longterm data. *J Rheumatol, 38*(8), 1552-1562. doi:10.3899/jrheum.100995

Launois, R., Avouac, B., Berenbaum, F., Blin, O., Bru, I., Fautrel, B., . . . Combe, B. (2011). Comparison of Certolizumab Pegol with Other Anticytokine Agents for Treatment of Rheumatoid Arthritis: A Multiple-treatment Bayesian Metaanalysis. *The Journal of rheumatology, 38*, 835-845. doi:10.3899/jrheum.100665

Liao, K., & Bykerk, V. (2011). All That Glitters Is Not Gold - Standardizing Diagnosis in Rheumatoid Arthritis Studies. *The Journal of rheumatology, 38*, 1223-1224. doi:10.3899/jrheum.110466

Medeiros, M. M., de Oliveira, B. M., de Cerqueira, J. V., Quixadá, R. T., & de Oliveira Í, M. (2015). Correlation of rheumatoid arthritis activity indexes (Disease Activity Score 28 measured with ESR and CRP, Simplified Disease Activity Index and Clinical Disease Activity Index) and agreement of disease activity states with various cut-off points in a Northeastern Brazilian population. *Rev Bras Reumatol, 55*(6), 477-484. doi:10.1016/j.rbr.2014.12.005

Pope, J., & Combe, B. (2013). Unmet Needs in the Treatment of Rheumatoid Arthritis. *Open Journal of Rheumatology and Autoimmune Diseases, 03*, 65-78. doi:10.4236/ojra.2013.32011

Tosh, J., Wailoo, A., Scott, D., & Deighton, C. (2011). Cost-Effectiveness of Combination Nonbiologic Disease-Modifying Antirheumatic Drug Strategies in Patients with Early Rheumatoid Arthritis. *The Journal of rheumatology, 38*, 1593-1600. doi:10.3899/jrheum.101327

van Vollenhoven, R., Emery, P., Bingham, C., Keystone, E., Fleischmann, R., Furst, D., . . . Rao, R. (2010). Longterm Safety of Patients Receiving Rituximab in Rheumatoid Arthritis Clinical Trials. *The Journal of rheumatology, 37*, 558-567. doi:10.3899/jrheum.090856

Yamasaki, T., Oda, R., Imai, K., Taniguchi, D., Toyama, S., Seno, T., . . . Kubo, T. (2016). Efficacy of MRP8/14 as a Marker of Disease Activity in Rheumatoid Arthritis. *Open Journal of Rheumatology and Autoimmune Diseases, 06*, 34-39. doi:10.4236/ojra.2016.62006