Rheumatoid arthritis : costs, treatments, and novel targets for therapy development

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Dedication

I dedicate this paper to the people living with rheumatoid arthritis, who have to endure this disease every day. I would also like to dedicate this paper to my wife and family. Thank you for your continuous love and support.

Acknowledgments

I would like to thank my scholarly project advisor, Dr. Barbara Saltzman, Ph.D., M.P.H., for her guidance, support, and encouragement throughout the entire scholarly project process. I also thank Jolene Miller, MLS, AHIP, for her assistance with literature searchers and navigating literature databases.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder that affects ~0.5-1% of the population world-wide, and nearly 1.3 million adult Americans with women being affected more often than men (Curtis et al., 2015; Gibofsky, 2012). RA is associated with joint inflammation and destruction, autoantibody generation, and systemic physiologic effects (McInnes & Schett, 2011). Some of the common negatively affected organ systems include the musculoskeletal, cardiovascular, and pulmonary systems (McInnes & Schett, 2011). Cartilage destruction occurs through dysregulation of the synovium and subsequent enzyme release that alters the collagen matrix. Chondrocytes, the cartilage matrix regulatory cells, are also decreased which leads to loss of surface cartilage (McInnes & Schett, 2011). Bone erosion occurs through cytokine activation of osteoclasts, which can breakdown mineralized tissues and allow for increased inflammatory cell occupancy (Lewiecki, 2009; McInnes & Schett, 2011). Moreover, the repair mechanisms of bone in RA is limited possibly due to various inhibitory mediators that limit synovial mesenchymal stem cell differentiation into chondroblasts or osteoblasts (Diarra et al., 2007; McInnes & Schett, 2011). The resulting bone breakdown may contribute to the development of bone disorders, such as osteoporosis (Wegierska et al., 2016). Thus, an understanding of the pathogenesis of bone erosion in RA patients may provide insight into treatment development and mitigation of other associated skeletal disorders.

The serious cardiovascular risks associated with RA have been reported. It has been suggested that the physiologic changes in RA including increased pro-inflammatory cytokines, immune complex development, acute phase reactants, and modified lipids may play a role in elevated rates of myocardial infarction and heart failure seen in RA patients (Holmqvist et al., 2010; McInnes & Schett, 2011; Solomon et al., 2003). Furthermore, the occurrence of interstitial

lung disease has also been recognized in RA (Restrepo et al., 2015). These systemic effects may be even further compounded by the potential for adverse side effects from the currently available RA treatments. In addition to the physiological effects, patients also experience the financial burden of this disease through costs of treatment, decreased productivity at work (presenteeism), and absenteeism from work. Moreover, it is estimated that RA is associated with $8.4 billion in health care costs annually (Curtis et al., 2015). Therefore, it is important to understand RA pathogenesis, evaluate the current therapies, consider the financial implications, and explore new potential targets for treatment.

Literature Review

Pathogenesis of RA

Like many diseases, the pathogenesis of RA involves both genetic and environmental factors. For instance, individuals with specific human leukocyte antigen (HLA)-DRB1 variants have been shown to be more susceptible to the development of RA (Kim et al., 2015). This genetic risk factor has been associated with patients that are identified as seropositive RA or rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) positive. Under both genetic and environmental influences (e.g., cigarette smoking), changes in post-transcriptional regulation lead to self-protein citrullination, which involves deimination of an arginine to a citrulline residue (Gibofsky, 2012; McInnes & Schett, 2011). This post-translational modification reduces immune tolerance to these proteins and, as a result, autoantibodies such as ACPA develop (Gibofsky, 2012; McInnes & Schett, 2011). RF is another autoantibody that targets the immunoglobulin Fc region, and may develop during the disease process of RA. It has been suggested that as a result of infection, immune complexes may induce RF, which can further contribute to RA pathogenesis and may even be used for diagnosis (McInnes & Schett, 2011).

Both the innate and adaptive immune systems contribute to the pathogenesis and clinical manifestations of RA. For instance, the innate system contributes to synovial inflammation via leukocyte migration and infiltration (Gibofsky, 2012; McInnes & Schett, 2011). This cell recruitment occurs through endothelial activation and cytokine and adhesion molecule up-regulation (McInnes & Schett, 2011). Macrophages, which are localized in the synovial membrane, are activated by a variety of mediators including toll-like receptors (TLR), nucleotide-binding oligomerization domain-like receptors, cytokines, T cell interaction, and

several other mechanisms (Liew & McInnes, 2002; McInnes & Schett, 2011; Seibl et al., 2003). Activated macrophages participate in phagocytosis, antigen presentation, as well as produce and release a variety of molecules including reactive oxygen intermediates, nitrogen intermediates, matrix-degrading enzymes, and cytokines. Correspondingly, the pro-inflammatory mediator, tumor necrosis factor (TNF)-α, and interleukins (e.g., IL-1, 6, 12, 15, 18, and 23) are among some of these cytokines (McInnes & Schett, 2011). Other innate immune cells, such as neutrophils and mast cells may also promote synovitis through a variety of pathways (Cedergren, Forslund, Sundqvist, & Skogh, 2007; Hueber et al., 2010).

The adaptive immune response is a key component in the induction of RA pathogenesis since autoantibodies (e.g., ACPA and RF) are generated to target modified proteins, which as a result, may be involved in downstream signaling cascades (Gibofsky, 2012). Moreover, the role of T cells in RA has been established. Elevated levels of dendritic cells and macrophages in the synovial membrane, promote the activation of T cells through cytokines, HLA class II molecules, and costimulatory mediators (e.g., CD80/86) (Gibofsky, 2012; Lebre et al., 2008; McInnes & Schett, 2011). This T cell activation promotes further downstream signaling pathways involved in inflammation. One subset of T helper cells, type 17 helper T cells, are of importance due to their release of IL-17A and TNF-α, which work together to influence fibroblast and chondrocyte activation as well as promote inflammation (Chabaud, Fossiez, Taupin, & Miossec, 1998; Chao et al., 2011; McInnes & Schett, 2011; Miossec, Korn, & Kuchroo, 2009). Other cytokines (e.g., transforming growth factor β, IL-1β, 6, 21, and 23) released from macrophages and dendritic cells mitigate regulatory T cell (Treg) differentiation, and contribute to type 17 helper T cell differentiation (McInnes & Schett, 2011). Moreover, in the pro-inflammatory synovial fluid, IL-17 releasing Treg cells function as type 17 helper T

cells, which further promotes inflammation (Bellucci et al., 2016; Wang et al., 2015). T cells may also perpetuate the pathogenesis of RA through the activation of macrophages and fibroblasts in a contact-mediated mechanism (McInnes, Leung, & Liew, 2000).

The humoral pathway is also indicated in the disease process of RA. B cells differentiate, in the synovium, into plasma cells which release autoantibodies and contribute to immune complex formation, complement activation, and promote inflammation through cytokine release (Gibofsky, 2012; McInnes & Schett, 2011). Furthermore, Th9 cells, which produce IL-9, may support B cell differentiation, proliferation, and antibody production (Ciccia et al., 2015). One study showed that patients with RA demonstrated an increased level of Th9 cells and IL-9 expression in the synovia of RA patients, which indicates a potential role for Th9 cells in the pathogenesis of RA (Ciccia et al., 2015).

The complex signaling pathways and cell interplay associated with RA indicates that there are several signaling mediators involved in the disease process. For instance, following T cell induced activation, macrophages and fibroblasts release pro-inflammatory cytokines such as, TNF-α, IL-1, IL-6, which stimulates other inflammatory mediators, thus contributing to cell recruitment to the synovial tissue (Scott & Kingsley, 2006). TNF-α contributes to the disease process, in part, by suppressing Treg cells, inducing endothelial-cell adhesion molecules, enhancing expression of various cytokines and chemokines, and contributing to the survival of fibroblast-like synoviocytes (Feldmann, Brennan, & Maini, 1996; McInnes & Schett, 2011). RA altered fibroblast-like synoviocytes demonstrate elevated levels of cytokines, chemokines, matrix metalloproteinases (MMPs), adhesion molecules, and tissue inhibitors of metalloproteinases (TIMPs), which may promote inflammation, cartilage damage, and T and B immune cell survival (Bradfield et al., 2003; Gibofsky, 2012; McInnes & Schett, 2011). Additionally, TNF-α has also

been shown to contribute to osteoclast differentiation and activation resulting in bone erosion (Schett & Teitelbaum, 2009). IL-6 is another cytokine that is expressed at high levels in the sera of RA patients (Feldmann et al., 1996; Park, Yoo, Kim, Cho, & Kim, 2016). IL-6 mediates Th17 cell generation, B cell maturation and differentiation, and osteoclast development (Park et al., 2016). Interestingly, in a recent study by Park et al. (2016) it was demonstrated that urinary IL-6 may be used as a non-invasive prognostic biomarker for the radiographic progression of RA.

The vast number of mediators involved in the RA disease process, as outlined above, implies the complexity of RA. The mechanisms discussed are not intended to be all inclusive. However, several of the important players involved in RA pathogenesis have been highlighted.

Systemic Effects of RA

RA may also exhibit its negative effects beyond the joints (Roubille & Haraoui, 2014; Wasserman, 2011). Two potentially serious extra-articular manifestations of RA involve the pulmonary and cardiovascular systems. The lungs are one of the possible sites for extra-articular involvement in RA (Bellucci et al., 2016). A disorder termed RA-related interstitial lung disease (RA-ILD) may be observed in 60% of patients (Bellucci et al., 2016). Although the complete mechanism of RA-ILD is still unclear, it has been suggested that smoking is an environmental risk factor that may contribute to the development of RA-ILD in genetically susceptible individuals (Restrepo et al., 2015). One study demonstrated that CD19(+)TGFβ(+) B regulatory cell levels were decreased in patients with RA-ILD, which suggests a possible mechanism involved in the development of RA-ILD (Guo, Zhang, Qin, & Wang, 2015). Although smoking has been considered an environmental risk factor for RA-ILD, a population based study by Bongartz et al. (2010) showed that RA-ILD risk is significantly higher among RA patients compared with non-RA controls after adjusting for several factors including smoking. The researchers found that older age of diagnosis, male gender, elevated erythrocyte sedimentation rate (ESR) levels, destructive changes, erosions, rheumatoid nodules, degree of functional status, and treatment with methotrexate (MTX) or corticosteroids were statistically significant risk factors associated with RA-ILD development (Bongartz et al., 2010). The same study also demonstrated a significantly decreased survival rate in RA-ILD patients as compared to expected survival rate matched to patients of the same gender and age (Bongartz et al., 2010). Together these findings suggest that RA-ILD is a serious extra-articular manifestation of RA with several potentially associated risk factors. Thus, further research focusing on the pathologic mechanism of RA-ILD is needed in order to limit the severe consequences of this associated disease.

Cardiovascular comorbidities are a known cause of mortality in RA (Bellucci et al., 2016). For instance, RA patients may be at an increased risk of endothelial dysfunction, atherosclerosis, venous thrombosis, congestive heart failure, and myocardial infarction (Di Minno et al., 2015; Mackey, Kuller, & Moreland, 2017; Nicola et al., 2006). In addition to traditional risk factors associated with cardiovascular disease (e.g., hypertension, diabetes, smoking, obesity, etc.), RA patients may also exhibit increased inflammatory markers such as C-reactive protein (CRP), ESR, TNF-α, and IL-6, which may contribute to systemic inflammation and thus cardiovascular disease symptoms (Mackey et al., 2017). Dyslipidemia, disease activity, and disease duration of > 10 years have also been shown to increase cardiovascular risk in RA patients (Mackey et al., 2017). To further establish the relationship between RA and cardiovascular disease, previous studies involving ultrasound measurement of arterial intima-media thickness (IMT) as a marker for atherosclerosis progression have been used (del Rincon et al., 2015). It has been shown that increased IMT is associated with elevated ESR, highlighting the importance of inflammation for potential atherosclerosis development in RA (del Rincon et al., 2015).

Current Treatments and Potential Side Effects

The American College of Rheumatology's (ACR) guidelines for the treatment of Rheumatoid Arthritis is used as a reference for guiding treatment of RA (Singh et al., 2016). These guidelines were generated from multiple systematic reviews of the available treatment options and the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. The ACR categorized patients as early RA, established RA, or high-risk comorbidities. Disease activity was rated as low, moderate, or high according to various instruments (e.g., scales and indices) used to evaluate disease activity and remission (Anderson et al., 2012). From the collected data, recommendations and treatment algorithms were developed by the ACR to help guide treatment (Figure 1 and 2). The proposed recommendations considered benefits versus harms from treatment, the quality of evidence, and patients' preferences. The current drug treatment categories consist of traditional disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor inhibitor (TNFi) biologics, non-TNFi biologics, glucocorticoids, and tofacitinib (Singh et al., 2016).

The traditional DMARDs include MTX, hydroxychloroquine (HCQ), leflunomide, and sulfasalazine. These drugs are frequently used as monotherapy or combination therapy for both early and established RA and are generally first line regimens. Although the mechanisms of action vary among these drugs, MTX is considered the preferred initial treatment for early and established RA (Singh et al., 2016; Wasserman, 2011). Several other DMARDs such as, azathioprine, cyclosporine, minocycline, and gold compounds, have been used in the past, but their use is infrequent and data focusing on these drugs since 2012 is limited (Singh et al., 2016).

DMARDs may also be categorized as biologic agents (Wasserman, 2011). Biologic medications are developed through recombinant DNA techniques, and are generated by living

cells (American College of Rheumatology, 2016). Two subcategories of biologic medications consist of TNFi and non-TNFi. TNFi biologics include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. These drugs work by inhibiting the effects of TNF (Curtis & Singh, 2011). The ACR guidelines suggest that TNFi be used in combination with MTX if moderate or high disease activity of RA persists despite DMARD monotherapy (Singh et al., 2016). The non-TNFi biologics consist of abatacept, rituximab, tocilizumab, and anakinra. However, anakinra is not frequently used for RA and evidence for its use has been limited since 2012 (Singh et al., 2016). As an alternative to TNFi, Non-TNFi biologics are also suggested with MTX when RA disease activity remains moderate or high despite the use of DMARD monotherapy. Tofacitinib is an alternative drug treatment of moderate or high disease activity in persistent established RA despite DMARD monotherapy, and may be used with or without MTX. Tofacitinb is a synthetic drug that inhibits Janus Kinase (JAK) enzyme activity, thus modulating the immune response (Fearon, Canavan, Biniecka, & Veale, 2016). In addition to the treatments listed above, short-term glucocorticoid therapy (<3 months) may be utilized with RA flares. Although not specified in the 2015 ACR guidelines, nonsteroidal anti-inflammatories (NSAIDs) may also be considered for short-term treatments (Wasserman, 2011). It is worth noting that drug combinations may need to be modified or adjusted according to the response to therapy and a treat to target strategy (i.e., lowest disease activity or remission) should be the treatment goal (Singh et al., 2016).

Although the current RA treatments may help to ameliorate joint inflammation and reduce immobility, they also have several potentially adverse side effects which requires routine monitoring (Curtis & Singh, 2011; Scott & Kingsley, 2006; Wasserman, 2011). For instance, MTX treatment has been associated with interstitial lung disease (as mentioned previously),

infection, hepatotoxicity, and spontaneous abortion and/or birth defects (Cipriani, Ruscitti, Carubbi, Liakouli, & Giacomelli, 2014; Levy, de Jesus, de Jesus, & Klumb, 2016; Pavy et al., 2006; Roubille & Haraoui, 2014). MTX-induced acute lung disease in RA patients has long been established (Cannon, Ward, Clegg, Samuelson, & Abbott, 1983). Symptoms of dyspnea, non-productive cough, and fever are generally the first symptoms of MTX induced pneumonitis that develop after starting low dose MTX treatment in RA patients (Roubille & Haraoui, 2014). These clinical features are likely due to infection or immunoallergic pneumonitis (Pavy et al., 2006). A recent systematic literature review corroborated previous findings that MTX is associated with an increased risk for pneumonitis (Roubille & Haraoui, 2014). However, the authors also discussed the findings from other systematic reviews which showed a relatively low occurrence (less than 1%) of MTX induced pneumonitis (Kinder et al., 2005; Roubille & Haraoui, 2014; Salliot & van der Heijde, 2009). Nevertheless, the occurrence of MTX induced pneumonitis is of importance since it may have a negative impact on patients with pre-existing lung disease or RA associated ILD, which may be an extra-articular manifestation of RA (Bongartz et al., 2010). Also, considering that MTX is the preferred first line treatment of RA, it is important to screen patients (e.g., chest radiograph and lung function tests with diffusing capacity of carbon monoxide) for any associated lung diseases prior to starting MTX (Pavy et al., 2006).

Hepatotoxicity is another potentially adverse side effect of MTX therapy. MTX has been shown to increase liver transaminase levels and persistently elevated levels in RA patients may indicate a potential for fibrosis or cirrhosis (Pavy et al., 2006; Price, James, & Deighton, 2010; West, 1997). Moreover, MTX treatment combined with alcohol consumption may increase the risk for liver fibrosis (Cipriani et al., 2014; Price et al., 2010). It has also been suggested that

patients be tested for hepatitis B and hepatitis C prior to beginning MTX therapy due to the potential increased risk of MTX-induced liver toxicity in patients with hepatitis B or C. However, data regarding the correlation between MTX and hepatitis B and C in liver toxicity is still unclear (Pavy et al., 2006). Therefore, in patients receiving MTX treatment the ACR recommends laboratory monitoring, including serum liver transaminases, every 2-4 weeks in the first 3 months of treatment, every 8-12 weeks during 3-6 months of treatment, and every 12 weeks if treatment is beyond 6 months (Singh et al., 2016). It is worth noting that side effects from MTX may be mitigated with the supplementation of folic acid or folinic acid. Studies have shown decreases in the occurrence of MTX discontinuation due to elevated liver transaminases and overall safety profile of MTX when supplemented with folic acid or folinic acid (Shiroky et al., 1993; van Ede et al., 2001). The use of folic acid or folinic acid is important in decreasing the adverse effects of MTX, but it is yet another medication added to the treatment regimen of RA. Spontaneous abortion and serious birth defects (e.g., microcephaly, hydrocephaly, and limb hypoplasia) have also been recognized with the use of MTX (Levy et al., 2016). Therefore, MTX should not be used in childbearing women who are pregnant or trying to become pregnant. This is a significant concern since a major portion of patients with RA are female. Despite the potentially concerning side effects of MTX, it is still considered the mainstay of RA treatment due to its efficacy and relatively low occurrence of adverse effects.

Other commonly prescribed DMARDS for RA have potentially serious side effects. For instance, HCQ has been associated with agranulocytosis and retinopathy (e.g., irreversible loss of central vision) (Ding, Denniston, Rao, & Gordon, 2016; Sames, Paterson, & Li, 2016). Although the occurrence of these serious adverse effects is rare, it may deter patients from using HCQ as a beneficial treatment option (Ding et al., 2016). Like MTX, leflunomide has been associated with

interstitial lung disease and elevated levels of hepatic aminotransferases as well as birth defects in animal studies (Gupta, Bhatia, & Gupta, 2011; Levy et al., 2016; Roubille & Haraoui, 2014). Furthermore, it has been shown that sulfasalazine may cause gastrointestinal effects (e.g. nausea and vomiting), central nervous system effects (e.g., dizziness and headache), oligospermia, and rash (Plosker & Croom, 2005). Even though the adverse effects of sulfasalazine may not be considered very serious, they may be significant enough to decrease treatment adherence.

In addition to conventional DMARDS, biologics are another important class of drugs that are indicated in the treatment of RA. The primary side effect of biologics is the risk for serious infections due to their immunosuppressive effect (Curtis & Singh, 2011). Several studies have been conducted to compare the occurrence of infection among the different drugs in this class. A randomized placebo controlled study by Keystone et al. (2004) showed that patients receiving adalimumab with MTX reported a greater proportion of serious infections (i.e., infections requiring hospitalization or intravenous antibiotic treatment) than placebo with MTX. Primary tuberculosis, histoplasmosis, herpes zoster with subsequent encephalitis, were among the serious infections reported (Keystone et al., 2004). A related study showed statistically significant rates of serious infections using the biologic infliximab with MTX therapy compared to placebo with MTX (Clair et al., 2004). Pneumonia and tuberculosis were listed as serious infections that occurred with the infliximab with MTX treated patients. These findings further corroborate the established understanding that TNFi biologics may increase the risk of latent tuberculosis reactivation (Keane et al., 2001). A systematic review and meta-analysis investigating the occurrence of serious infections and malignancies in TNFi treated RA reported an elevated risk for serious infections among these populations (Bongartz et al., 2006). The risk of serious infections has been researched with other non-TNFi biologics including rituximab, abatacept,

and anakinra. A meta-analyses of randomized placebo-controlled trials involving these agents demonstrated that only high dose anakinra may increase risk for serious infection in RA (Salliot & van der Heijde, 2009). However, the authors suggested that a lack of statistical power for the abatacept and rituximab groups may limit the ability to completely disregard infectious risk associated with these agents (Salliot & van der Heijde, 2009).

Risk for malignancy in RA patients treated with TNFi has also been suggested over the years (Curtis & Singh, 2011). In the same study mentioned earlier, risk for malignancy in TNFi treated RA patients was analyzed in addition to serious infections (Bongartz et al., 2006). Infliximab and adalimumab were evaluated and the researchers concluded that there is a dose-dependent increase risk for developing malignancy (Bongartz et al., 2006). Conversely, other studies did not demonstrate an increased risk for malignancy in TNFi treated RA compared with non TNFi RA (Askling et al., 2005; Setoguchi et al., 2006; Wolfe & Michaud, 2007). Therefore, the increased risk for malignancy in TNFi biologic treated RA needs to be further evaluated.

The Economic Impact of RA

In addition to the physically debilitating symptoms, the economic impact of RA has been an area of concern for patients and employers. A retrospective, observational study investigated the economic influence of RA through medical expenditures, short-term disability benefit costs, and absenteeism costs on nine large U.S. employers (Ozminkowski, Burton, Goetzel, Maclean, & Wang, 2006). The study compared 8,502 employees with RA to 8,502 employees without RA using a propensity score matching process based off of the following variables: demographics, comorbidity patters, prescription medication, location, type of health plan, index year, and employer (Ozminkowski et al., 2006). This propensity score process generates study populations (e.g., employees with RA vs. employees without RA) that are more balanced for comparison. The patients were compared for 12 months following the index date, which was determined by the date of the initial medical claim documenting an RA diagnosis. The results of the study showed that RA employees acquired $4,087 of medical expenditures (e.g., inpatient, outpatient, and pharmacy expenditures) more than the non-RA employees over the 12 month study period (Ozminkowski et al., 2006). However, absenteeism costs and short term disability costs only increased ~$27 and $129 respectively. These findings indicate that RA employees have a higher economic burden than non-RA employees and that medical expenditures have the most significant impact on this increased cost (Ozminkowski et al., 2006). The researchers also utilized previous studies to compare the economic burden (e.g., medical expenditure, absence costs, and short-term disability costs) of RA to other illnesses, such as renal failure, heart disease, bipolar disorder, any cancer, depression, diabetes, chronic obstructive pulmonary disease, low back disorders, hypertension and asthma (Ozminkowski et al., 2006). It was determined that the total cost of RA, over a twelve month period, was greater than all of the

aforementioned diseases except for renal failure. It is worth noting that when the researchers adjusted for disease prevalence, RA moved to the fourth most expensive disease behind depression, hypertension, and heart disease (Ozminkowski et al., 2006). Nonetheless, these results demonstrate the substantial costs associated with RA, even when compared with several other medical conditions. Thus, it is important to recognize the economic impact of RA and to develop treatment strategies to reduce the cost burden for RA patients and employers.

Other studies have explored the occurrence of work disability related to RA (Allaire, Wolfe, Niu, & Lavalley, 2008; Wolfe & Hawley, 1998; Yelin, Henke, & Epstein, 1987). For instance, Allaire et al. (2008) investigated the prevalence and incidence of work disability in RA patients in the United States over the course of three years. Subjects were categorized using various factors such as, demographics and disease duration. The authors reported that the prevalence of premature work cessation increased with the duration of disease. It was also determined whether premature work cessation was attributed to arthritis specifically. Correspondingly, the prevalence of premature work cessation attributed to arthritis also increased with disease duration, although the percentage was lower than the prevalence of total premature work cessation. These findings imply that early treatment intervention for RA may help to decrease premature work cessation later in the disease course. Interestingly, the authors reported a lower prevalence of premature work cessation at 10 years of disease duration (35%) compared to the results of an earlier study by Yelin et al. (1987) (50%). One possible explanation for this difference may be due to the advancement of treatments since the two studies were published twenty years apart. However, premature work cessation in RA patients is still prevalent in the United States and has financial implications for individuals living with RA.

Treatment for RA can be expensive, especially when TNFi biologics are utilized. Depending on various factors, the annual cost for TNFi therapy per patient may be between $10,000 and $25,000 (Scott & Kingsley, 2006). Conflicting studies have differing views on whether TNFi biologics are cost effective for the treatment of RA (Scott & Kingsley, 2006). However, certain treatment regimens may improve the rate of absenteeism and presenteeism in RA patients. A randomized control trial by Smolen et al. (2006) measured the occurrence of absenteeism from work between RA patients receiving MTX versus MTX with infliximab (TNFi) over 54 weeks. The researchers categorized missed work days as: 0 days, 1-10 days, or > 10 days. The results showed that patients receiving MTX with infliximab had a significantly higher percentage of missed 0 days and a significantly lower percentage of missed 1-10 days and missed > 10 days compared with MTX treatment alone (Smolen et al., 2006). Correspondingly, another study assessed work productivity loss in RA patients receiving MTX compared to MTX with etanercept (TNFi) over 12 months (Anis et al., 2009). The study measured work productivity loss due to absenteeism and presenteeism as follows: 1) number of missed workdays, 2) reduced working time, and 3) the number of stopped workdays. The results demonstrated that the MTX with etanercept group had a significantly lower mean occurrence in all three measures as compared to the MTX group alone (Anis et al., 2009). Collectively, these studies show that, although biologic TNFi are expensive for the treatment of RA, they may be cost-effective since they reduce the number of missed work days through mitigating the debilitating symptoms of RA.

Another study compared the cost effectiveness of several different first-line biologics for the treatment of moderate-to-severe RA using an administrative claims-based effectiveness algorithm to a geographically diverse commercially insured U.S. population (Curtis et al., 2015).

The researchers evaluated the cost effectiveness of abatacept and infliximab (intravenous biologics), and adalimumab, etanercept, and golimumab (subcutaneous biologics) over the course of one year following the date of the initial claim (Curtis et al., 2015). The results showed that the one-year costs of biologic treatment per person was higher for the intravenous biologics compared to subcutaneous biologics. This may be partially due to the increased cost associated with intravenous administration. Furthermore, the researchers calculated the biologic cost per effectively treated patient and found that patients receiving subcutaneous biologic treatment had lower costs per effectively treated patient as compared to intravenous biologic treated patients. Specifically, etanercept was deemed the most cost-effective followed by golimumab, adalimumab, abatacept, and infliximab. Although etanercept was the most cost effective, the mean cost per patient over the course of a year was approximately $14,385 with the cost of infliximab being $19,283. In addition, the overall effectiveness of first-line biologic therapy was only 28.9% in the first year of treatment of moderate-to-severe RA (Curtis et al., 2015). Thus, the results indicate that certain biologics may be more cost-effective than others. However, biologic therapy can be expensive and may take a prolonged period of time before treatment is effective. The findings further support the need for development of treatments that are cost-effective, primarily in the early stages of RA.

Presenteeism or reduced productivity at work due to ill health has been investigated in the RA population (Verstappen, 2015). Various questionnaires and indices have been used to evaluate presenteeism in RA patients. Like absenteeism, studies have shown that RA patients treated with biologic therapy reported a significant reduction in presenteeism (Kavanaugh et al., 2009; Pavelka et al., 2013). However, the number of studies focusing on presenteeism is limited and further research is needed to determine treatment efficacy at reducing presenteeism.

New Targets for Treatment

Due to the multiple mediators involved in RA pathophysiology, there are several potential targets for novel drug development. Receptor activator of nuclear factor kappaB ligand (RANKL) has been an area of research over recent years. This ligand may bind to receptor activator of nuclear factor kappaB (RANK) on the surface of preosteoclasts and osteoclasts, leading to differentiation, activation, and cell survival (Lewiecki, 2009). As a result of RANK activation, bone resorption is enhanced which may potentially result in osteoporosis and the erosive symptoms associated with RA (Hofbauer & Schoppet, 2004). Denosumab is a RANKL antibody that inhibits binding to RANK and has been FDA approved for the treatment of postmenopausal osteoporosis. However, the use of denosumab in the management of RA is still being investigated. A phase II clinical trial evaluated the efficacy of denosumab on structural damage, bone mineral density, and bone turnover in active erosive RA patients receiving MTX (Cohen et al., 2008). The researchers reported that denosumab increases bone mineral density, halts the escalation of bone erosion scores, and mitigates the appearance of bone turnover markers. A later study exhibited similar results demonstrating resistance against erosion and increased bone mineral density, as measured by dual x-ray absorptiometry, magnetic resonance imaging, and radiography, in the the hand of RA patients (Deodhar et al., 2010). A 2016 Japanese phase II clinical trial reported that denosumab decreased the rate of bone erosion and increased the bone mineral density (regardless of glucocorticoid use) in RA patients being treated with MTX (Takeuchi et al., 2016). This study also showed that the adverse effects among treatment groups and placebo were comparable. Collectively, these studies indicate that denosumab may be a new alternative or additional treatment option to decrease the progression of joint damage seen in RA.

It has been shown that the synovial joint in RA exists in a hypoxic environment due to synovial hyperplasia and immune cell infiltration, which further promotes the need for oxygen to the joint (Hua & Dias, 2016). Angiogenesis is one physiologic mechanism adapted to address this oxygen demand. However, studies have shown that oxygen perfusion, via new vessel formation, may be inadequate to meet the oxygen demand (Kennedy et al., 2010). Hypoxia-inducible factor (HIF) is a transcription factor that promotes cell survival in response to hypoxia (Hua & Dias, 2016). Specifically, the HIF-1α subunit of this heterodimeric transcription factor is modulated by oxygen levels (Hua & Dias, 2016). The RA synovium expresses elevated levels of HIFs in synovial macrophages, fibroblast-like synoviocytes, and osteoclasts (Ryu et al., 2014). Although HIFs are an adaptive response to hypoxia, they may enhance the disease process in RA. For instance, HIF-α may regulate cytokines, chemokines, MMPs, adhesion molecules, toll-like receptors, and growth factors involved in inflammation, angiogenesis, cartilage damage, and bone erosion (Hua & Dias, 2016). One study demonstrated that, in RA synovial fibroblasts, HIF-1α can increase the expression of various pro-inflammatory cytokines (e.g., TNF-α, IL-6/8, IL-1β), specific cell-cell contact mediators, and stromal cell-derived factor-1 (chemokine that is elevated due to hypoxia) (Hu et al., 2016; Santiago et al., 2011). The researchers also reported that inhibiting HIF-1α in RA synovial fibroblasts reduced IFN-γ, IL-17, and IgG production (Hu et al., 2016). In addition, the HIF signaling pathway is involved in angiogenesis under hypoxic environments, such as a synovial joint in RA (Hua & Dias, 2016). HIF induces the expression of vascular endothelial growth factor (VEGF), which is a proangiogenic mediator (Elshabrawy et al., 2015; Maruotti, Cantatore, & Ribatti, 2014). This new vessel development may contribute to the inflammation by transporting immune cells to the synovial site. Furthermore, the upregulated proangiogenic mediators (e.g. VEGF) can disrupt the normal regulation of angiogenesis, which

creates a pathologic environment that further contributes to synovial inflammation (Maruotti et al., 2014). Although angiogenesis is increased, the oxygen demand persists and hypoxia occurs leading to generation of reactive oxygen species (ROS) (Hua & Dias, 2016; Kennedy et al., 2010). This increase in ROS exceeds endogenous antioxidant defenses and may result in oxidative damage to DNA, proteins, and lipids (Kennedy et al., 2010; Mateen, Moin, Khan, Zafar, & Fatima, 2016). Interestingly, HIF-1α has been shown to be a mediator of ROS generation in response to hypoxia (Hua & Dias, 2016; Kennedy et al., 2010). Since the HIF pathway has been shown to enhance pro-inflammatory cytokines, promote VEGF expression and angiogenesis, and contribute to ROS generation, it may be a potential target for future therapy development in RA. In a study by Li, Qin, and Du (2015), the anti-inflammatory effects of andrographolide, a component of the herbaceous plant *Andrographis paniculata*, on RA fibroblast like synoviocytes under hypoxic conditions were investigated. Since *Andrographis paniculata* extract has previously been shown to provide relief in RA patients, the researchers explored the specific effects of andrographolide (Burgos et al., 2009; Li et al., 2015). It was found that andrographolide blocked the hypoxia induced HIF-1α expression of mRNA and protein as well as reduced HIF-1α DNA binding ability (Li et al., 2015). These results indicate that the effect of andrographolide on inhibiting HIF-1α should be further examined as a novel treatment option in RA patients.

As previously mentioned, VEGF is an important mediator of angiogenesis, and its inhibition may be important in attenuating the damage associated with angiogenesis in RA. A medical hypothesis article suggested that Itraconazole, an FDA approved antifungal drug that plays a role in inhibiting angiogenesis, may be beneficial for the treatment of RA (Sheikh, Naqvi, Naqvi, & Sheikh, 2012). Previous studies have shown that Itracanazole can inhibit angiogenesis

in non-small cell lung cancer *in vivo* and *in vitro* models in response to VEGF and basic fibroblast growth factor (Aftab, Dobromilskaya, Liu, & Rudin, 2011). Additionally, Itracanazole is an interesting potential drug for RA since it is already FDA approved and relatively inexpensive (Sheikh et al., 2012). However, large scale clinical trials are needed to evaluate whether Itracanazole may be used as a therapeutic agent for RA (Sheikh et al., 2012).

The role of ROS induced damage in RA has been suggested as a contributor to the chronicity of the disease (Mateen, Moin, Khan, et al., 2016). A recent study showed elevated levels of ROS, lipid peroxidation, DNA damage, and protein oxidation in the blood samples isolated from RA patients (Mateen, Moin, Khan, et al., 2016). The same study also reported diminished antioxidant defenses, which is consistent with other studies (Seven, Guzel, Aslan, & Hamuryudan, 2008). Therefore, therapies focusing on limiting oxidative damage in RA may provide new insight into symptom relief. One study evaluated the effect of antioxidant supplementation (combination of vitamins A, C, and E) with conventional RA treatment on glutathione, thiol, and vitamin C (endogenous antioxidants) status in RA patients (Jaswal, Mehta, Sood, & Kaur, 2003). The researchers also evaluated malondialdehyde (MDA) concentration, which is an indicator of oxidative stress. After 12 weeks of treatment, glutathione, thiol, and vitamin C levels in the blood were higher in the antioxidant supplementation with conventional therapy group versus the conventional therapy group alone. Lower levels of MDA, as compared with conventional therapy alone, were also reported in this group.

A separate study investigated the effect of the antioxidant coenzyme Q_{10} supplementation in RA patients with moderate and severe disease activity (Abdollahzad, Aghdashi, Asghari Jafarabadi, & Alipour, 2015). Coenzyme Q_{10} has been shown to protect cell membranes and proteins against oxidative stress and enhance endogenous antioxidant defenses (Abdollahzad et

al., 2015; Bentinger, Tekle, & Dallner, 2010). Furthermore, coenzyme Q_{10} has exhibited anti-inflammatory properties through suppressing the pro-inflammatory marker, IL-6, in coronary artery disease patients (Lee, Huang, Chen, & Lin, 2012). Abdollahzad et al. (2015) reported that two months of oral supplementation of coenzyme Q_{10}, in addition to conventional treatment, in RA patients significantly decreased serum MDA and TNF-α level compared to the placebo group. It is worth noting that coenzyme Q_{10} did not have a significant effect on decreasing IL-6 or increasing total antioxidant capacity. However, the investigators postulated that this may be due to inadequate dosing or duration of coenzyme Q_{10} supplementation. Future studies focusing on coenzyme Q_{10} as a supplement to conventional RA therapy should be further investigated since it may limit the oxidative and inflammatory damage associated with RA. The studies outlined above provide evidence that the addition of antioxidant supplementation to conventional therapy for RA may provide additional therapeutic benefits especially in reducing oxidative stress.

Plant derived polyphenols have also been considered as a therapeutic option in RA due to their antioxidant and anti-inflammatory characteristics (Ahmed, Anuntiyo, Malemud, & Haqqi, 2005; Mateen, Moin, Zafar, & Khan, 2016). It has been reported that curcumin exhibits its anti-inflammatory effect, in part, by decreasing expression of IL-6 and VEGF from fibroblast like synoviocytes isolated from synovial tissue of RA patients (Kloesch, Becker, Dietersdorfer, Kiener, & Steiner, 2013). In a 2012 clinical trial pilot study, the effects of curcumin (a type of polyphenol) on active RA patients was studied (Chandran & Goel, 2012). Curcumin was compared with diclofenac, an NSAID used for relief of RA symptoms. The researchers used the disease activity score (DAS) 28, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analog scale (VAS), and the ACR criteria to assess efficacy of the treatment after 8 weeks.

Safety was monitored using vital signs, physical examination, and lab studies. It was determined that curcumin was safe and effective at improving the DAS and ACR scores alone or in addition to diclofenac in RA patients (Chandran & Goel, 2012). The curcumin only group showed the most improvement and was also the only group to significantly improve CRP. Although this was a pilot study, the results suggest that curcumin may be a supplemental or alternative treatment to RA. However, future studies are needed to definitively determine curcumin's applicability in RA. Other naturally derived compounds such as resveratrol, emodin, genistein, and kaempferol have been studied in RA (Mateen, Moin, Zafar, et al., 2016). The anti-inflammatory and/or anti-oxidant effects of these compounds provides promising areas of research for a better understanding of RA pathogenesis and future treatments.

As mentioned earlier, cytokines play a major role in the pathogenesis of RA. Several of the currently established therapies such as, TNFi biologics and non TNFi biologics target specific cytokines involved in RA. However, the efficacy of these medications may be limited in certain individuals and the potential for serious adverse effects warrants the need for new cytokine targets. As previously discussed, the role of the inflammatory cytokine IL-17 in RA is an area of continuing research. Clinical trials focusing on IL-17 monoclonal antibodies have been conducted for the treatment of RA. A meta-analysis was performed to evaluate the safety and efficacy of anti-IL-17 therapy in the RA population (Kunwar, Dahal, & Sharma, 2016). Seven studies ranging from the year 2010 to 2015 were analyzed. The researchers used the ACR20/50/70 method to measure anti-IL-17 efficacy compared to placebo. Adverse events were determined from the studies to evaluate safety of treatment. It was determined that anti-IL-17 therapy significantly improved RA symptoms as measured by ACR20 and 50 (Kunwar et al.,

2016). As a result of these findings, anti-IL-17 therapy for the treatment of RA may be a promising area of drug development.

Research focusing on limiting the disease process of RA should also consider the potential cardiovascular effects of RA since it is a major cause of morbidity and mortality. Studies investigating the efficacy of angiotensin-converting enzyme inhibitors (ACEI) on limiting cardiovascular disease in RA has been conducted (Flammer et al., 2008). It is recognized that ACEI may be associated with lower levels of ROS, decreases in nuclear factor-κB pathway, and enhancements in endothelial function and fibrinolysis (Dohi, Criscione, Pfeiffer, & Luscher, 1994; Flammer et al., 2008; Hamdan, Quist, Gagne, & Feener, 1996; Hernandez-Presa et al., 1997; Zhang et al., 1999). These effects may limit the development of atherosclerosis. A randomized, double-blind, cross over study evaluated the effects of ramipril (ACEI) on oxidative stress, inflammation, and vascular activity in moderate RA patients over the course of 8 weeks (Flammer et al., 2008). It was determined that endothelial function was enhanced and plasma TNF-α and CD40 (inflammatory marker) levels decreased following ramipril treatment (Flammer et al., 2008). It is worth noting that other inflammatory markers, such as IL-1, IL-6, myeloperoxidase, C-reactive protein, and blood sedimentation rate were not affected by ramipril treatment. However, the improvements in endothelial function in this study highlight the need for future research focusing on limiting cardiovascular disease in RA patients.

The potential role of TNFi therapy on cardiovascular risk has also been investigated. Previous research has shown that compared with patients starting on non-biologic DMARD therapy, patients starting TNFi therapy may demonstrate beneficial effects on reducing cardiovascular risk in the first 6 months (Solomon et al., 2013). In this study, however, improvement in cardiovascular risk in the TNFi therapy group diminished by 12 months and the

beneficial effects were only noted for patients ≥65 years of age (Solomon et al., 2013). Thus, further research is needed to determine the beneficial effects of TNFi therapy on cardiovascular risk.

Discussion

This literature review was conducted to explore the pathogenesis of RA, evaluate the current therapeutic options, and investigate new potential targets for development of novel therapeutics. The past and current research regarding these areas of study is expansive. Numerous studies focusing on the efficacy and safety of the current treatments for RA have been conducted. As outlined in the literature review, the potential for serious adverse effects ranging from interstitial lung disease to spontaneous abortion and birth defects are present and a concern for patients with RA. The individual medications used for RA have specific adverse effects, but the risk of infection is apparent with all of the current treatments (e.g., conventional DMARDs and biologics). This is likely due to the immunosuppressive activity of the current treatment options. Moreover, according to ACR's current guidelines for RA treatment, drug combination therapy may be needed to increase treatment efficacy in patients who may not respond to monotherapy. The beneficial effect of a multi-drug approach on limiting symptom severity may be noted, however, the combination of these immunosuppressive medications may increase the occurrence of serious infection according to previous studies (Clair et al., 2004; Keystone et al., 2004). Collectively, the side effects of current RA therapy may not only contribute to other acute illnesses, but they may also potentially limit the patient's adherence to treatment. Although there is a potential for serious adverse effects, the occurrence may be relatively low, such is the case of MTX induced pneumonitis. Additionally, screening measures may be used to detect any pre-existing medical conditions prior to starting treatment and/or to evaluate response to treatment. Moreover, periodic monitoring of patients utilizing history, physical exam, lab results, and imaging may help to limit the occurrence of potential adverse effects.

Another major concern is the economic impact of RA due to the debilitating symptoms of the disease process. Patients are not only at increased risk for premature work cessation and decreased work productivity, but the financial costs associated with RA are great even when compared to several other chronic illnesses (e.g., hypertension and diabetes). For instance, TNFi biologics are one of the mainstays of RA treatment, but they are expensive. The studies outlined in the literature review demonstrated improvements in absenteeism in patients treated with TNFi biologics, which implies their potential cost effectiveness. However, it is important to consider that the duration of these studies (Anis et al., 2009; Smolen et al., 2006). Both studies evaluated absenteeism over the course of roughly one year, which may not be long enough to determine if treatment is truly cost effective. Also, the patient's response to treatment may change with disease duration and/or the patient may feel that their condition is getting better prompting them to stop taking their medication. Both of these scenarios could result in a RA flare requiring treatment modifications and/or supplemental treatment such as, corticosteroids leading to increased costs. Additionally, the studies listed above only focused on comparing etanercept and infliximab with methotrexate plus placebo. Thus, certain biologics may be more cost effective than others. As mentioned earlier Curtis et al. (2015), compared several different first-line biologics and determined that cost effectiveness varied among each of them. Furthermore, the researchers showed that the overall efficacy in the first year of treatment with these therapies was around 30% (Curtis et al., 2015). Specific treatment should be tailored to the individual patient in order to enhance the cost effectiveness. Moreover, the possibility of RA associated systemic effects such as, cardiovascular disease and interstitial lung disease may increase the economic burden of RA if medications are not specifically addressing the effects of possible comorbidities. Collectively, in order to improve cost effectiveness, the provider and patient should maintain

good communication regarding disease status, therapy efficacy, and financial limitations throughout the duration of the disease. Future research should further evaluate the cost effectiveness of RA therapy, with specific consideration of long-term studies.

Due to the potential adverse effects and cost of the current treatment options, other targets for treatment were explored in the literature review. Furthermore, the extra-articular effects of RA may promote the development of other illnesses which can worsen the patient's condition. The new targets for therapy development outlined above suggest alternative pathways for improving the symptoms and disease severity of RA. One such pathway involved mitigating the potential for bone erosions through the use of denosumab. The studies discussed above all showed increased bone mineral density with denosumab. Yet, Takeuchi et al. (2016) did not observe any difference in RA disease activity between the denosumab and placebo groups. This limited effect on RA disease activity may be due to the short duration of the trial (12 months). However, the researchers reported comparable safety profiles between the denosumab and placebo groups (Takeuchi et al., 2016). Correspondingly, since this drug has already been FDA approved for treatment of postmenopausal osteoporosis, it should be considered for decreasing the occurrence of osteoporosis in patients with RA. Further studies evaluating the long term effects of denosumab should be considered.

Research focusing on HIF-1α in RA is promising since attenuating this transcription factor may limit pro-inflammatory cytokines, VEGF, and ROS all of which may contribute to the pathogenesis of RA. Li et al. (2015), showed decreased migration and invasion of RA synovial fibroblasts under hypoxic conditions by limiting HIF-1α through the use of andrographolide. Since this study was conducted using synovial tissue isolated from RA patients, further clinical trials focusing on safety and efficacy are needed before andrographolide can be

considered as a therapeutic option. In addition to HIF-1α, ROS levels in RA may also be attenuated using antioxidant supplementation. The studies discussed above suggested the use of vitamins A, C, and E as well as coenzyme Q_{10} (Abdollahzad et al., 2015; Jaswal et al., 2003). Jaswal et al. (2003) demonstrated enhanced antioxidant parameters and lower oxidative stress in both the conventional treatment group as well as the conventional treatment group with antioxidant supplementation as compared to the control group. However, these results were enhanced in the antioxidant supplementation group indicating the potential advantage for antioxidant supplementation in RA patients. Abdollahzad et al. (2015) determined that coenzyme Q_{10} supplementation effectively reduce overexpression of serum TNF-α as well as MDA (indicator of oxidative stress). However, IL-6 and TAC were not significantly affected. These may indicate the presence of several mediators involved in the disease process of RA. Additionally, this discrepancy may be attributed to the short duration of the study. It is worth noting that although both studies provided evidence at either reducing various pro-inflammatory and/or oxidative stress markers, neither group evaluated the functional status or symptom severity of the patients. Future studies on antioxidant supplementation should consider comparing oxidative damage with symptom severity. This may provide greater insight into the beneficial effects of antioxidant supplementation in RA.

The role of polyphenols has also been discussed above. Interestingly, curcumin showed greater improvements in DAS and ACR scores compared with diclofenac sodium (NSAID) group (Chandran & Goel, 2012). Moreover, curcumin was generally safe reporting mild adverse events in this group. Although this study shows promising results, the small sample size and short duration of the study warrants additional research. Also, this study compared curcumin with diclofenac sodium which is not an ideal first line therapy for RA (e.g., MTX).

Thus, studies regarding curcumin's beneficial effects in RA patients should include increased sample size, longer duration, and comparison with multiple DMARDs or biologics to determine its safety and efficacy.

Another potential target for treatment of RA is IL-17. The meta-analysis conducted by Kunwar et al. (2016) provided encouraging evidence for anti-IL-17 therapy in RA. Yet, the researchers reported an increased risk of infection with anti-IL17 therapy. This finding is not exactly unexpected due to the suspected immunomodulatory effects of anti-IL-17 therapy. However, due to the limited number of studies analyzed, further research is needed to evaluate the safety and efficacy of anti-IL-17 therapy in RA.

The increased risk for cardiovascular disease in RA patients warrants investigation into potential treatments focusing on extra-articular effects. As mentioned previously, Flammer et al. (2008) reported beneficial effects of ACEI treatment in RA patients. The reported increased endothelial function and decreased levels of plasma TNF-α following ACEI treatment, suggests that TNFi biologics may have an additional beneficial effect on the cardiovascular system. Therefore, future research investigating therapeutic options for cardiovascular disease in RA should not only explore the therapeutic effects of ACEIs, but also further evaluate TNFi therapy on cardiovascular risk in RA.

Conclusion

The numerous mediators involved in the pathogenesis of RA indicates the complexity of this disease. Several of the available treatment options focus on decreasing disease severity through mitigating inflammation. Although the current therapies may be effective at improving disease activity, their cost and potential for serious adverse effects are concerning. Correspondingly, other targets for therapy development are being explored. These alternative strategies may provide new or additional therapeutic options. Furthermore, the economic impact of RA is apparent. RA is correlated with heightened medical expenditures, occurrence of absenteeism, and work cessation. Future studies focused on improving the cost-effectiveness of treatment may result in mitigating the financial burden associated with RA.

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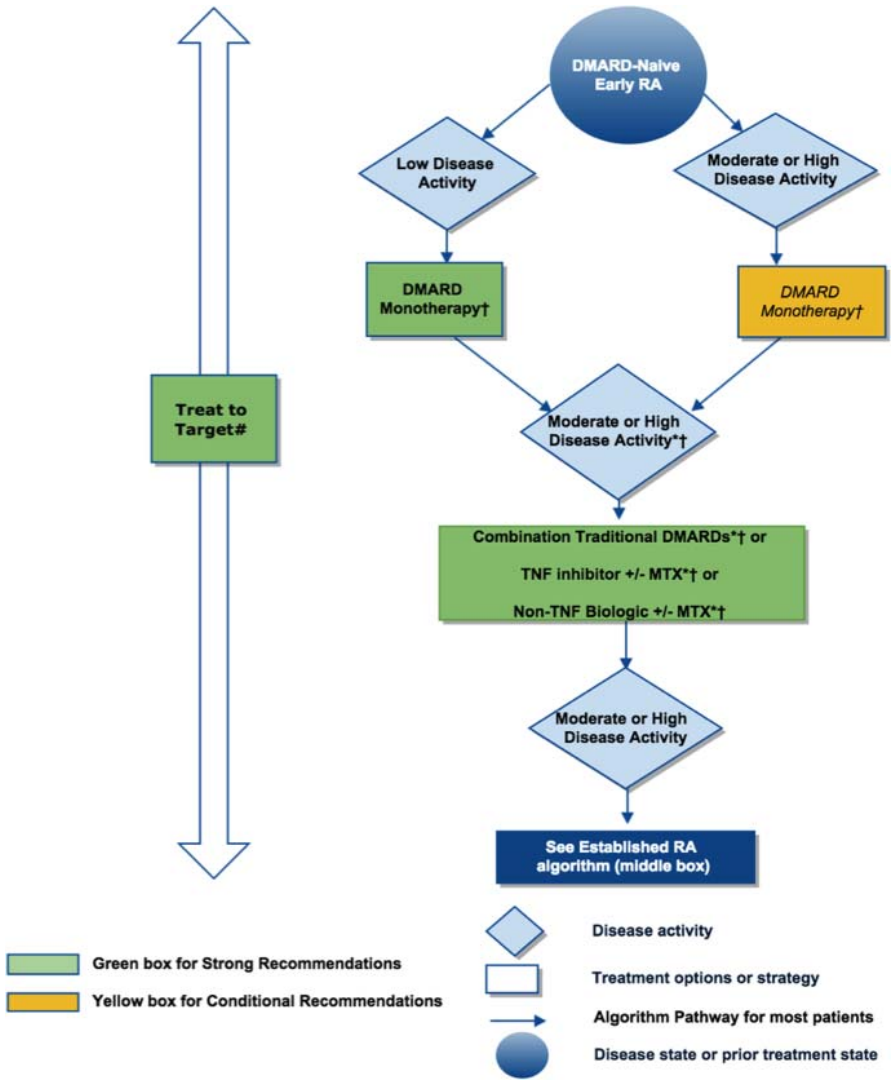
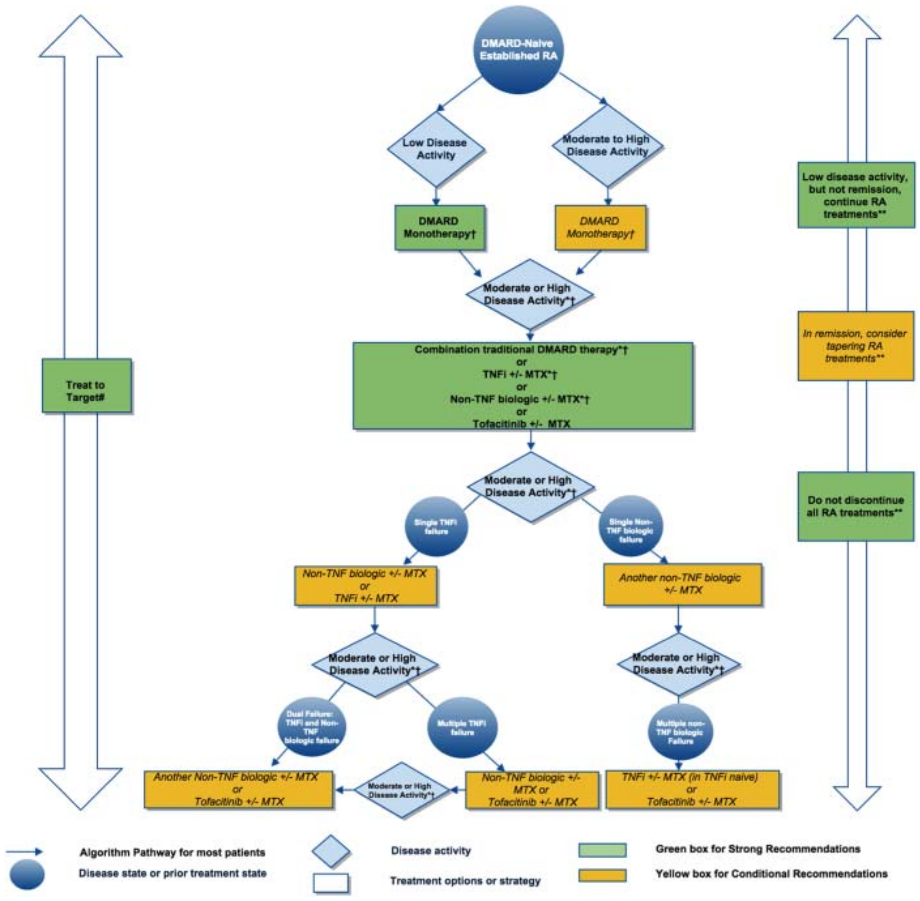


2015 American College of Rheumatology recommendations for the treatment of Early rheumatoid arthritis (RA), defined as disease duration <6 months. ∗ = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions A.1 to A.12. MTX = methotrexate.

Figure 1. The algorithm shows the recommended treatment guidelines for DMARD-naïve early RA according to the ACR. From 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, by Singh et al. (2016). *Arthritis Care & Research*, 68, 9. 2015. Reprinted with permission.



2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA), defined as disease duration ≥6 months, or meeting the 1987 ACR classification criteria . Due to complexity of management of established RA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show the key recommendations. For a complete list of recommendations, please refer to the Results. ∗ = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting traditional disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. ** = tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions B.1 to B.38. MTX = methotrexate; TNFi = tumor-necrosis factor inhibitor.

Figure 2. The algorithm shows the recommended treatment guidelines for DMARD-naïve established RA according to the ACR. From 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, by Singh et al. (2016). *Arthritis Care & Research*, 68, 12. 2015. Reprinted with permission.

Abstract

Objective. Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that can have debilitating effects on the body and impose significant financial costs. This literature review outlines several mediators of RA pathogenesis, evaluates the current treatments, assesses the economic impact, and explores possible targets for novel therapy development. **Method.** The databases PubMed and Thomson Reuters Web of Science were utilized for collecting literature. **Results.** 102 articles were identified consisting of original research, clinical trials, randomized control trials, meta-analyses, observational studies, clinical research/review studies, cohort studies, systematic reviews, literature reviews, case reports and medical hypotheses. **Conclusion.** RA is a multifaceted disease with negative physiologic implications and a substantial economic burden on both patients and employers. Current treatments may be limited due to the cost and potential for serious adverse effects. The alternative strategies for therapy development outlined in this review provide new or supplemental therapeutic options for consideration.