International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

MANAGEMENT OF EARLY RHEUMATOID ARTHRITIS

Dr. Majesh Pratap Malla* and Dr. She Yuan Ju

Department of Orthopaedics, Clinical Medical College of Yangtze University, Jingzhou Central Hospital, Jingzhou, Hubei Province, PR China

ABSTRACT

Rheumatoid arthritis (RA) is characterized by persistent synovitis, systemic inflammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide. Multiple risk factors are involved in the causation of Rheumatoid arthritis of which Genetic factors, smoking are the common ones. This disease mostly affects women population and frequently seen in elderly group of population. Damage to the affected joint, disability, decreased quality of life, and cardiovascular and other comorbidities are the major complications of this disease. The prognosis for the patient with newly diagnosed RA has dramatically changed over the past two decades. Early diagnosis and treatment with the goal of remission or low disease activity have shown to achieve remission while taking drugs. . Disease-modifying anti-rheumatic drugs (DMARDs), the key therapeutic agents, reduce synovitis and systemic inflammation and improve function. The natural history of RA can easily be altered if early diagnosis and aggressive treatment is done. The early management of RA will clearly prevent the complications associated. Biological agents are used when the arthritis is uncontrolled or toxic effects of DMARDs occur. Tumor Necrosis Factor (TNF) Inhibitors are the first biological agents which then are followed by abatacept, rituximab, tocilizumab. These biological agents are expensive and may cause infections. Thus the use of these drugs is quite restricted. This review article focuses on the benefits of early diagnosis and management of RA so as to prevent the complications.

INTRODUCTION

Rheumatoid Arthritis is a clinical syndrome spanning several disease subsets[1]. Several inflammatory cascades are involved which all lead to a final common pathway where a persistent synovial inflammation and associated articular cartilage and bone damage occurs [2]. RA is 3 times more frequent in women than men. The prevalence rises with age and is seen highest in women older than 65 years. This suggests that hormonal factors could have a pathogenic role [3]. Prevalence of RA varies geographically [4, 5]. Different genetic risks and environmental exposures also play role in its prevalence. Smoking is the dominant environmental risk factor and doubles the risk of developing Rheumatoid arthritis [6]. Other potential environmental risk factors include alcohol, coffee, vitamin D status, oral contraceptive use, and low socio-economic status [7].

Strong evidence exists that early diagnosis and aggressive treatment alter the natural history of RA. Prevention of permanent structural damage to joints, including both erosions and joint-space narrowing as measured on radiographs, but also the prevention of deformities that can occur without erosions, is a strong rationale for early treatment [8, 9]. Functional impairment occurs when the structural damage reaches to a critical level. In some cases there have been evidences of healing of the erosions but joint-space narrowing and subluxations are permanent [10-13]. A meta- analysis of 12 studies demonstrated significant reduction of radiographic progression in patients treated early when compared with the subjects treated later. Patients with more aggressive erosive disease benefited the most from early therapy [14]. Many of the large trials in early disease show a strong correlation of disease duration to outcomes [15-17]. Some investigators have suggested a presence of window of opportunity in early disease during which therapy is somehow particularly effective. There is no place for argument that earlier the treatment, better the outcome. However the window concept should always not be carried too far. It would be a wrong assumption that the patients do not benefit once this window of opportunity is closed. There are data which suggest that patients with active disease have been benefitted from appropriate DMARD treatment regardless of disease duration [18-23].

DISCUSSION

Earlier is better, but how soon is soon enough? There is really no fixed answer to this question. However the goal should be set as to start the treatment within the 3 months of onset of disease. Benefits achieved from the very early therapy of RA have highlighted the need to make the diagnosis of RA as soon as possible. The American College Of Rheumatology (ACR) 1987 criteria [24] had poor sensitivity and specificity for classification of patients with early inflammatory arthritis as having RA [25]. Identification of individuals with early arthritis who subsequently develop RA was failed [26]. Hence to overcome these concerns, the ACR and EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) collaborated to devise new classification criteria

for early arthritis [27]. A new set of criteria that were meant to distinguish inflammatory arthritis from non-inflammatory arthritis which assess joint involvement, autoantibody status and acute phase response and symptom duration was made. The results were the ACR-EULAR 2010 classification criteria **Table 1.** The goal of the new criteria was to provide a uniform approach to identify individuals with undifferentiated synovitis who have the highest probability of developing persistent RA and structural damage and therefore individuals who would benefit from early DMARD intervention. The new classification criteria will also allow more uniform disease definition and subject recruitment into clinical and epidemiologic studies in early RA.

1. Joint involvement (0 – 5)
    - ❖ 1 medium to large joint (0)
    - ❖ 2 to 10 medium to large joints (1)
    - ❖ 1 to 3 small joints (large joints not counted) (2)
    - ❖ 4 to 10 small joints (large joints not counted) (3)
    - ❖ More than 10 joints (at least one small joint) (5)

2. Serology (at least 1 result is needed for classification) (0-3)
    - ❖ Negative RF and negative ACPA (0)
    - ❖ Low-positive RF or low positive ACPA (2)
    - ❖ High positive RF or high positive ACPA (3)

3. Acute- phase reactants (at least 1 result is needed for classification) (0-1)
    - ❖ Normal CRP and normal ESR (0)
    - ❖ Abnormal CRP or abnormal ESR (1)

4. Duration of symptoms (0-1)
    - ❖ < 6 week (0)
    - ❖ >= 6 week (1)

Table 1: The 2010 ACR- EULAR classification for RA

RF = Rheumatoid Factor, **ACPA** = AntiCitullinated Protein Antibody, **CRP** = C - reactive protein and **ESR** = Erythrocyte Sedimentation Rate

Imaging in diagnosing Rheumatoid arthritis:

Radiography of hands and feet readily identify the juxta-articular erosions that characterize the progressive establishment of rheumatoid arthritis and which are irreversible. Two such typical erosions are sufficient for diagnosis [28]. Inadequately controlled disease is characterized by extensive damage on radiographs. Rapid progression of joint damage needs intensive treatment. New imaging modalities, particularly Ultrasound and MRI, can assess irreversible structural changes [29, 30].

Anti- CCP in early diagnosis of RA:

Studies have shown the presence of autoantibodies in people who have no symptoms or physical findings of arthritis but who will develop RA later in life [31-38]. The most important of these are Anti- CCP. It has been shown that Anti- CCP is reasonably sensitive and highly specific for RA [39-43]. Van Galen et al. [44] have demonstrated that the presence of Anti-CCP antibodies predicts the progression of undifferentiated arthritis to RA independently. This shows the value and usefulness of this test in patients with undifferentiated inflammatory arthritis.

What is Preclinical RA?:

It is now clear that people who later develop RA often have anti-ccp antibodies and RF antibodies present in their serum years before they develop clinical RA. The questions are how to identify these people and what risks of therapy are acceptable in these people who do not have yet the clinical disease? So another argument which also can be made regarding the early treatment is that the disease can be prevented by treating or modifying the risk factors in these people [45] [46-49]. Since RA has a prevalence of only 1 % CCP used in the general population may not be a good screening test, even if it has high sensitivity. Also the chances of getting false positives would be higher than the true positives. However preventive trials are in the planning stages for people at high risk for the future development of RA.

Treatment of RA:

Different national and regional guidelines for management of rheumatoid arthritis exist, including recommendations from ACR, EULAR and the UK's National Institute for Health and Clinical Excellence [50-52].

Treatment of symptoms:

Analgesics reduce pain and Non-steroidal anti-inflammatory drugs (NSAIDs) lessen pain and stiffness. Both of these groups of drugs are widely used to treat the symptoms of RA. Supports for the use of NSAIDs are found to be stronger than the use of analgesics [53]. Yet these NSAIDs have lost their role as first-

line treatment due to the concerns about their limited effectiveness, inability to modify the long-term course of the disease, and the gastrointestinal and cardiac toxic effects [54, 55].

DMARDS:

Disease – modifying antirheumatic drugs (DMARDs) are the mainstay of treatment for RA [56]. These drugs reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function. Methotrexate is the dominant DMARD. Other widely used drugs are Sulfasalazine and Leflunomide. Hydroxychloroquine and chloroquine have DMARD-like propertied. GOLD and cyclosporine are additional DMARDs.

DMARDs are also sometimes combined. Several combinations of DMARDs have proven their efficacy [57]. One of the examples is Methotrexate, Sulfasalazine and hydroxychloroquine (triple therapy).

Nausea, hepatotoxicity, blood dyscrasias, and interstitial lung disease are the adverse side effects of DMARDs [58, 59].

Biological agents:

Biological agents include the drugs like TNF inhibitors, abatacept, rituximab, and tocilizumab. These are combined with methotrexate. This combination reduces antibody formation [60] as well as increases the efficacy [61]. These are administered as self-injected twice weekly to monthly or given by infusion.

Reactions and infections at injection sites are common side effects. There have been reports of increased risk of tuberculosis with TNF inhibitors use [62].

Glucocorticoids:

Short- term glucocorticoids reduce synovitis. In long term they reduce joint damage[63]. These can be used in 2 settings. Firstly, short term use during flare-ups in disease. Secondly, intra-articular glucocorticoids are highly effective for local treatment of active joints [64].

Other supportive treatments:

Exercise, joint protection, foot care, and psychological support are other supportive non-pharmacological treatments [65]. The co-morbidities should also be addressed. These include cardiac disease, bone disease, and depression. Other systemic diseases like Sjogren's syndrome, ling disease, and vasculitis, need specific treatment. Surgical management like joint replacement may prove to be vital to maintain the function when the joint fails.

CONCLUSION

Therapeutic goals and the ability to measure them are critically important in treating any disease. This certainly is true in RA treatment also. The key treatment aim should be remission or sustained low disease. This goal can be achieved with DMARD monotherapy, combinations of DMARDs, and DMARD-biological combinations. The best therapy for each individual patient should always be selected. The next major advance in treatment in early RA will occur when differential selection can identify which patients will benefit most from which therapies and perhaps which patients are at risk for toxicities from the therapies.

REFERENCES

1. van der Helm-van Mil, A.H. and T.W. Huizinga, *Advances in the genetics of rheumatoid arthritis point to subclassification into distinct disease subsets.* Arthritis Res Ther, 2008. **10**(2): p. 205.
2. van Oosterhout, M., et al., *Differences in synovial tissue infiltrates between anti-cyclic citrullinated peptide-positive rheumatoid arthritis and anti-cyclic citrullinated peptide-negative rheumatoid arthritis.* Arthritis Rheum, 2008. **58**(1): p. 53-60.
3. Symmons, D., et al., *The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century.* Rheumatology (Oxford), 2002. **41**(7): p. 793-800.
4. Costenbader, K.H., et al., *Geographic variation in rheumatoid arthritis incidence among women in the United States.* Arch Intern Med, 2008. **168**(15): p. 1664-70.
5. Biver, E., et al., *Low and stable prevalence of rheumatoid arthritis in northern France.* Joint Bone Spine, 2009. **76**(5): p. 497-500.
6. Carlens, C., et al., *Smoking, use of moist snuff, and risk of chronic inflammatory diseases.* Am J Respir Crit Care Med, 2010. **181**(11): p. 1217-22.
7. Liao, K.P., L. Alfredsson, and E.W. Karlson, *Environmental influences on risk for rheumatoid arthritis.* Curr Opin Rheumatol, 2009. **21**(3): p. 279-83.
8. Smolen, J.S., et al., *Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing.* Ann Rheum Dis, 2009. **68**(10): p. 1535-40.
9. Sokka, T., et al., *Erosions develop rarely in joints without clinically detectable inflammation in patients with early rheumatoid arthritis.* J Rheumatol, 2003. **30**(12): p. 2580-4.
10. Aletaha, D., J. Funovits, and J.S. Smolen, *Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction.* Ann Rheum Dis, 2011. **70**(5): p. 733-9.
11. Smolen, J.S., et al., *Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials.* Ann Rheum Dis, 2010. **69**(6): p. 1058-64.
12. van der Heijde, D., et al., *Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial.* Ann Rheum Dis, 2008. **67**(9): p. 1267-70.
13. Drossaers-Bakker, K.W., et al., *Long-term course and outcome of functional capacity in rheumatoid*

arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum, 1999. **42**(9): p. 1854-60.

14. Finckh, A., et al., *Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis.* Arthritis Rheum, 2006. **55**(6): p. 864-72.
15. Kyburz, D., et al., *The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study.* Rheumatology (Oxford), 2011. **50**(6): p. 1106-10.
16. Anderson, J.J., et al., *Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration.* Arthritis Rheum, 2000. **43**(1): p. 22-9.
17. Nell, V.P., et al., *Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis.* Rheumatology (Oxford), 2004. **43**(7): p. 906-14.
18. Garnero, P., et al., *Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone.* Arthritis Rheum, 2010. **62**(1): p. 33-43.
19. Heiberg, M.S., et al., *Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study.* Ann Rheum Dis, 2006. **65**(10): p. 1379-83.
20. Maini, R.N., et al., *Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis.* Arthritis Rheum, 1998. **41**(9): p. 1552-63.
21. Smolen, J.S., *Efficacy and safety of the new DMARD leflunomide: comparison to placebo and sulfasalazine in active rheumatoid arthritis.* Scand J Rheumatol Suppl, 1999. **112**: p. 15-21.
22. Takeuchi, T., et al., *Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients--REACTION 52-week study.* Rheumatology (Oxford), 2011. **50**(10): p. 1908-15.
23. Tanaka, Y., et al., *Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study.* Ann Rheum Dis, 2012. **71**(6): p. 817-24.
24. Arnett, F.C., et al., *The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.* Arthritis Rheum, 1988. **31**(3): p. 315-24.
25. Banal, F., et al., *Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis.* Ann Rheum Dis, 2009. **68**(7): p. 1184-91.
26. Morvan, J., et al., *Changes over time in the diagnosis of rheumatoid arthritis in a 10-year cohort.* J Rheumatol, 2009. **36**(11): p. 2428-34.
27. Funovits, J., et al., *The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I.* Ann Rheum Dis, 2010. **69**(9):

p. 1589-95.

28. Thabet, M.M., et al., *The prognostic value of baseline erosions in undifferentiated arthritis.* Arthritis Res Ther, 2009. **11**(5): p. R155.
29. Boutry, N., et al., *Early rheumatoid arthritis: a review of MRI and sonographic findings.* AJR Am J Roentgenol, 2007. **189**(6): p. 1502-9.
30. Kubassova, O., et al., *Quantifying disease activity and damage by imaging in rheumatoid arthritis and osteoarthritis.* Ann N Y Acad Sci, 2009. **1154**: p. 207-38.
31. van der Woude, D., et al., *Epitope spreading of the anti-citrullinated protein antibody response occurs before disease onset and is associated with the disease course of early arthritis.* Ann Rheum Dis, 2010. **69**(8): p. 1554-61.
32. van de Stadt, L.A., et al., *Development of the anti-citrullinated protein antibody repertoire prior to the onset of rheumatoid arthritis.* Arthritis Rheum, 2011. **63**(11): p. 3226-33.
33. Koivula, M.K., et al., *Antibodies binding to citrullinated telopeptides of type I and type II collagens and to mutated citrullinated vimentin synergistically predict the development of seropositive rheumatoid arthritis.* Ann Rheum Dis, 2012. **71**(10): p. 1666-70.
34. Nielen, M.M., et al., *Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors.* Arthritis Rheum, 2004. **50**(2): p. 380-6.
35. Bos, W.H., et al., *Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study.* Ann Rheum Dis, 2010. **69**(3): p. 490-4.
36. Rantapaa-Dahlqvist, S., et al., *Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis.* Arthritis Rheum, 2003. **48**(10): p. 2741-9.
37. Chibnik, L.B., et al., *Comparison of threshold cutpoints and continuous measures of anti-cyclic citrullinated peptide antibodies in predicting future rheumatoid arthritis.* J Rheumatol, 2009. **36**(4): p. 706-11.
38. Shadick, N.A., et al., *C-reactive protein in the prediction of rheumatoid arthritis in women.* Arch Intern Med, 2006. **166**(22): p. 2490-4.
39. Nishimura, K., et al., *Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis.* Ann Intern Med, 2007. **146**(11): p. 797-808.
40. van Gaalen, F.A., et al., *Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis.* Arthritis Rheum, 2004. **50**(7): p. 2113-21.
41. Bas, S., et al., *Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibodies, anti-keratin antibodies and IgM rheumatoid factors.* Rheumatology (Oxford), 2002. **41**(7): p. 809-14.
42. Goldbach-Mansky, R., et al., *Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset.* Arthritis Res, 2000. **2**(3): p. 236-43.
43. Kroot, E.J., et al., *The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis.* Arthritis Rheum, 2000. **43**(8): p. 1831-5.

44. van Gaalen, F.A., et al., *Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study.* Arthritis Rheum, 2004. **50**(3): p. 709-15.
45. Bykerk, V.P., *Strategies to prevent rheumatoid arthritis in high-risk patients.* Curr Opin Rheumatol, 2011. **23**(2): p. 179-84.
46. Deane, K.D., J.M. Norris, and V.M. Holers, *Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation.* Rheum Dis Clin North Am, 2010. **36**(2): p. 213-41.
47. Gerlag, D.M., et al., *EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis.* Ann Rheum Dis, 2012. **71**(5): p. 638-41.
48. Kolfenbach, J.R., et al., *A prospective approach to investigating the natural history of preclinical rheumatoid arthritis (RA) using first-degree relatives of probands with RA.* Arthritis Rheum, 2009. **61**(12): p. 1735-42.
49. van de Sande, M.G., et al., *Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase.* Ann Rheum Dis, 2011. **70**(5): p. 772-7.
50. Saag, K.G., et al., *American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.* Arthritis Rheum, 2008. **59**(6): p. 762-84.
51. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.* Ann Rheum Dis, 2014. **73**(3): p. 492-509.
52. Deighton, C., et al., *Management of rheumatoid arthritis: summary of NICE guidance.* Bmj, 2009. **338**: p. b702.
53. Chen, Y.F., et al., *Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.* Health Technol Assess, 2008. **12**(11): p. 1-278, iii.
54. Scott, P.A., et al., *Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials.* Ann Rheum Dis, 2007. **66**(10): p. 1296-304.
55. Schaffer, D., et al., *Risk of serious NSAID-related gastrointestinal events during long-term exposure: a systematic review.* Med J Aust, 2006. **185**(9): p. 501-6.
56. Donahue, K.E., et al., *Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis.* Ann Intern Med, 2008. **148**(2): p. 124-34.
57. Choy, E.H., et al., *A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal.* Rheumatology (Oxford), 2005. **44**(11): p. 1414-21.
58. Salliot, C. and D. van der Heijde, *Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research.* Ann Rheum Dis, 2009. **68**(7): p. 1100-4.

59. Alcorn, N., S. Saunders, and R. Madhok, *Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing.* Drug Saf, 2009. **32**(12): p. 1123-34.
60. Svenson, M., et al., *Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies.* Rheumatology (Oxford), 2007. **46**(12): p. 1828-34.
61. Strangfeld, A., et al., *Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide.* Ann Rheum Dis, 2009. **68**(12): p. 1856-62.
62. Dixon, W.G., et al., *Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR).* Ann Rheum Dis, 2010. **69**(3): p. 522-8.
63. Kirwan, J.R., et al., *Effects of glucocorticoids on radiological progression in rheumatoid arthritis.* Cochrane Database Syst Rev, 2007(1): p. Cd006356.
64. Goossens, P.H., et al., *Reliability and sensitivity to change of various measures of hand function in relation to treatment of synovitis of the metacarpophalangeal joint in rheumatoid arthritis.* Rheumatology (Oxford), 2000. **39**(8): p. 909-13.
65. Hurkmans, E., et al., *Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis.* Cochrane Database Syst Rev, 2009(4): p. Cd006853.