Review Paper

BIOLOGICAL THERAPY FOR RHEUMATOID ARTHRITIS – AN UPDATE

Islam MF[1], Alim MA[2], Mia MAA[3], Razzak MA[4], Haque AFMS[5]

Abstract

Disease-Modifying Antirheumatic Drugs (DMARDs) play a vital role in the management of Rheumatoid Arthritis (RA). This update aims at focusing some important and novel aspects of biological DMARDs. Recent advances in biological therapy have opened a new window of opportunity for this potentially crippling disorder particularly patients refractory to conventional DMARDs. Close association of cytokine network in the pathophysiology of rheumatoid arthritis has facilitated the development of new biological agents and revolutionized the treatment. Novel drugs such as anti-tumor necrosis factor-alpha (anti-TNF-α) (eg, certolizumab), anti-interleukin-1 (anti-IL-1) (eg, anakinra), anti-interleukin-6 (anti–IL-6) (eg, tocilizumab), T-cell depletor (eg, abatacept), anti-cluster differentiation 20 (anti-CD-20) (eg, rituximab) have recently joined with the existing biological therapy in the arena of RA. Emerging agents like adhesion molecule inhibitors, anti-interleukin-15 (anti-IL-15), fusion protein-cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin G1 (CTLA4Ig) are also under investigations. Higher potency, quicker onset of action, less frequency of administration are the main advantages as opposed to potential serious side effects such as infection susceptibility, injection site reaction, Systemic Lupus Erythematosus-like (SLE-like) and Multiple Sclerosis-like (MS-like) symptoms and higher price. Combination of biologicals is not recommended because of higher rate of adverse events and lack of additive effects. But biological DMARDs in combination of Methotrexate (MTX) are now a preferred choice of many rheumatologists. The last but not the least option for aggressive and refractory patients of RA is biological DMARDs.

Key-words: Disease-modifying antirheumatic drugs (DMARDs), anti-tumor necrosis factor-alpha (anti-TNF-α), fusion protein-catatonic T-lymphocyte-associated antigen 4-IgG1 (CTLA4Ig).

Introduction

Disease-modifying antirheumatic drugs are the mainstay of treatment for rheumatoid arthritis. Permanent disability and premature deaths due to RA are potentially preventable. The previous conservative approach termed as therapeutic pyramid has been supplanted by early initiation & combination of DMARDs therapy[1]. Remissions of symptoms and preventing articular damage are the realistic therapeutic goals. Recent advances in understanding the cytokine network involved in the aetiopathogenesis of RA have led to the successful use of therapies that target TNF-α, IL-I, IL-6 and other inflammatory mediators[2]. Consequently biological DMARDs have emerged as an important and effective therapeutic strategy in the management of RA particularly in refractory and very aggressive cases[3]. Frequency of use of biological is also raising rapidly[4]. The aim of this review article is to focus some important and novel aspects of biological DMARDs.

Biological DMARDs

DMARDs are broadly divided into two groups[5]: Conventional/non-biologicals and biological DMARDs/biological response modifiers. Synovitis is the central to the pathophysiology of RA, which is largely attributable to biological mediators such as TNF-α, IL-I, IL-6, IL-15 and growth factors. Biological agents are the proteins derived by bioengineering technology that influence the inflammatory process and

1. **Col Md Faridul Islam**, MBBS, FCPS, Classifiedd Spl in Medicine, BNS, Patenga; 2. **Brig Gen (Retd) Md Abdul Alim**, MBBS, FCPS, FACP, Ex Chief Physician and Adviser Spl, CMH Dhaka; 3. **Brig Gen Md Abdul Ali Mia**, MBBS, MCPS, FCPS, Personal Physician to Honourable Prime Minister; 4. **Col Md Abdur Razzak**, MBBS, MCPS, FCPS, Classified Spl in Medicine & Rheumatologist, CMH, Comilla; 5. **Col AFM Shamsul Haque**, MBBS, MCPS, FCPS, Classified Spl in Medicine & Cardiologist, CMH, Dhaka.

inhibit the actions of cytokines. They modify the disease process, slow the joint damage, reduce radiographic deterioration dramatically and alter the laboratory parameters which measure the disease activities such as fall in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor titre and platelet count if they were raised previously.

Biologic products are: TNF-α antagonist (eg, infliximab, eterercept, adalimumab, certolizumab, golimumab), anti-IL-I (eg, anakinra), anti-IL-6 (eg, tocilizumab), T-Cell depletors (eg, abatacept), anti-CD20 (eg, rituximab). Other biologicals under investigation are[6]: tacrolimus, co-stimulation blockers, CTLA4Ig, antibiotics and gene therapy. Adverse effects of biologicals[7]: wider use of biological DMARDs has resulted in adverse events including infections, (tuberculosis, aspergillosis, listeriosis, cyto-megalovirus), injection-site and infusion reaction, cancer, vasculitis, SLE-like autoimmune diseases, MS-like demyelinating disorders, heart failure, liver disease, haematologic abnormalities including aplastic anaemia and lymphoma, severe allergy and aseptic meningitis. It is advised that biological should not be used in these conditions.

How cost effective are biologicals?[8] Biologicals are more expensive than conventional DMARDs. Costs range from $14000 to over a million US dollars per quality-adjusted life-year (QALY) gained.

Etanercept[9]: It is a soluble TNF-receptor fusion protein that binds to both TNF-α and TNF-β, thereby preventing interaction with its receptors. After subcutaneous administration, etanercept is absorbed slowly, with concentrations peaking at approximately 50 hours. A regimen of 50 mg once weekly appears to be as effective as a regimen of 25 mg twice weekly. It is used in severely active rheumatoid arthritis patients. It can be used in combination with MTX.

Infliximab[10]: clinical trials of infliximab have shown significant and clinically relevant improvements in active rheumatoid arthritis. In initial multi-centre, double-blind, placebo-controlled trials of infliximab infusion, substantial clinical response was noted. Subsequent multiple-infusion studies in patients with active disease despite MTX monotherapy confirmed the results of initial studies. Infliximab is available only as parenteral form. Its serum half-life of is variable and lengthy, ranging from 8.0 to 9.5 days. The dosing schedule is 3 mg/kg at weeks 0, 2 and 6, followed by maintenance dosing every 8 weeks and its approved regimen mandates combination therapy with MTX.

Adalimumab[11]: it is a recombinant human IgG1 monoclonal antibody that binds to human TNF-α with high affinity and specificity, both impairing cytokine binding to its receptors and lysing cells that express TNF-α on their surface. After subcutaneous administration, it is absorbed slowly, with peak concentrations reaching after approximately 130 hours. Adalimumab given as monotreatment to patients with longstanding, severe RA refractory to traditional DMARDs produces a rapid, sustained response and is safe and well tolerated; with no dose limiting side effects. It may be used both as monotreatment and as combination with MTX. Its dose is 40mg every second week.

Anakinra[12]: it is a recombinant form of human IL-1 receptor antagonist that targets the type I IL-1 receptor that is expressed in many tissues. It has a short half-life (6 hours); daily administration (100mg) is more effective than injections given weekly or three times a week. Anakinra, alone or in combination with MTX, has been more effective than placebo in randomized, controlled trials. The most common adverse event is dose dependent skin irritation at the injection site.

Indications for use of biologicals

Consensus recommendations from the American College of Rheumatiology(ACR)[13] and European League against Rheumatism (EULAR)[14], also based on systematic review & consideration of effectiveness are: 2 trials of 6 months of conventional DMARDs mono therapy or combination therapy (at least one including MTX) should fail to control symptoms or prevent disease progression before a biological is recommended. However, currently UK recommendations are that anti-TNF therapy should be initiated only in an active RA (Disease activity score 28>5.1) when an adequate trial of at least two other DMARDs (including methotrexate) has failed[15].

Advantages of biological over conventional DMARDs

Benefits of conventional DMARDs are usually delayed for about weeks to months, i.e., a delay of 1-6 months before a clinical response is evident, whereas onset of action in case of biological is only 1 to 2 weeks. They are more potent than conventional DMARDs. In some resistant cases, conventional DMARDs are not adequate to control active disease. In these cases, biological such as TNF-α antagonist should be added to MTX. If inflammatory disease is inadequately controlled, then ant-TNF-α should be started[16]. Biological can reduce radiological deterioration dramatically. Anti-TNF-α is efficacious in improving disease activities and in retarding radiological progression when used alone or in combination with MTX[17]. Traditional DMARDs modify systemic inflammatory process of RA by their impact on joint destruction. In contrast, biological have more specific cytokine targets. Patients of RA have high concentration of TNF-α in the synovial fluid. Antagonizing TNF-α is a viable therapeutic strategy[18].

How biological combination therapy?

By use of the therapeutic principles applied to oncology, hypertension, and infectious disease, in which several agents of different classes are used in combination, recent trials in rheumatoid arthritis have assessed the efficacy of combination DMARDs therapy for decreasing inflammatory symptoms and retarding joints destruction while maintaining a tolerable toxic-effect profile[19]. More recent studies have shown that combination therapy has clear benefits and tolerable toxic effects[20]. While biological DMARDs are often combined with non-biological in the treatment of RA, they are not used with other biological agents because of unacceptable risk of serious infections. Combination of biological are not recommended because of higher rate of adverse events and lack of additive effects[21]. Neither etanercept nor adalimumab requires co-prescription of MTX but combining either with MTX is more effective than either agent alone.

Efficacy and safety of bioligicals

A Cochrane network meta-analysis of 27 studies containing 7643 patients taking 6 biological (abatacept, adalimumab, anakinra, etanercept, infllximab and rituximab) published that 30% of patients discontinued biological and those who continued taking biological, maintained degree of American College of Rheumatology-50 (ACR-50) benefits over 5 years[22]. A Cochrane review and network meta-analysis of 163 randomized controlled trials showed that biological were associated with high rate of adverse events and withdrawn due to adverse effects and reactivation of tuberculosis[23].

How are biological taken and monitored?[24-26]

Initially treatment is started with MTX monotherapy or in combination with other non-biological DMARDs as soon as RA is diagnosed. Aim is to achieve a minimal target of remission or low disease activity. In the United Kingdom, if it fails after 2 trials of 6-month of traditional DMARDs, then a biological agent is added. Current practice would be to start with a TNF-α inhibitor and MTX. Patients of RA who have failed with anti-TNF-α should receive a different biological. Patients are initially monitored frequently until target remission or low-disease activity is achieved, then every 4-month, with key measures of disease activity, response and adverse effects. Patients should be periodically monitored by clinical and laboratory parameters such as complete blood count, liver function test, urea,creatinine.

What might the future holds for biological?

Different combinations of biological may achieve a more complete shutting down of inflammation & joint damage; however,increased rates of infection have been seen with abatacept plus etanercept[27], and anakinra plus etanercept[28]. Systemic inflammation is hypothesized to increase cardiovascular risk in patients with RA, and whether biological provide cardioprotection requires further study[29]. However, it needs long term data on benefits and safety of different biological.

Conclusion

Biological treatment for RA continues to advance rapidly and many new drugs such as pegylated soluble TNF receptor antagonist, anti-IL-15, adhesion molecule inhibitors, stem cell transplantation and gene therapy are under investigations. These and other advances in future will lead to an improved quality of life for people with RA.

References

1. THE LANCET, 15 September 2001. 358(9285):903-911.doi:10.1016/so140-6736 (01)06075-5.

2. Jemes R, O'Dell. Therapeutic Strategies for Rheumatoid Arthritis. N Engl J Med 350; 25 June 17, 2004.

3. Rheumatoid arthritis drugs in development- mayo Clinic. Com. Updated March 31, 2005.

4. Scott DL, Kingsley GH.TNF-α inhibitors for RA. N Engl Med 2006; 355: 704-12.

5. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996; 39: 713-22.

6. Rheumatoid arthritis drugs in development- mayo Clinic. Com. Updated March 31, 2005.

7. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med 2004 350; 2167-79.

8. Schoels M, Wong J, Scott DL. Economic aspects of treatment portions in RA. Ann Rheum DIS 2010; 69: 996-1004.

9. ACP Journal Club, 2001 Jul-Aug: 135:2 Bathon JM, Martin RW, Fleischmann RM. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000 Nov 30; 343: 1686-93.

10. Charles PJ, Smmenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies 100. Rheumatoid arthritis drugs in development- mayo Clinic. Com. Updated March 31, 2005.

11. LBA VD. Efficacy and safety of the fully human anti-tumour nerosis factor-α monoclonal antibody adalimumab (D2F7) in DMARD refractory patients with RA. ANN Rheum Dis 2003; 62:1168-77.

12. Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol 1998; 16:27-55.

13. Saag KG, Teng GG, Curtis JR. ACR 2008 recommendations for use of non-biological DMARD in RA. Arthritis Rheum 2008; 59:762-84.

14. Smolen JS, Landewe R, Breedveld FC, Emery P. EULAR recommendations for management of RA with synthetic and biological DMARD. Ann Rheum DIS 2010; 69:964-75.

15. Doherty M, Ralston SH. Musculoskeletal disease. In: Colledge NR, Walker BR, Ralston SH. editors. Davidson's principles & Practice of Medicine 21st ed. Edinburgh London New York Philadelphia Sydney Toronto: Churchill Living stone; 2010. P.1081.

16. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum 2003; 48:313-8.

17. Tugwell p, pincus T, Yocum D. Combination therapy with cyclosporine and methotrexate in severe RA. N Engl J Med 1995; 333: 137-41.

18. Keffer J, Probert L, Cazlaris H. Transgeneic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J 1991; 10; 4025-31.

19. Wilke WS. Scherrer YR. Clough JD. Combination chemotherapy for severe rheumatoid arthritis. Methotrexate in patients with rheumatiod arthritis. Rheum 1994; 37:5361. Intern Med specialist 1989; 10:59-76.

20. Srott DL, Dawes PT, Tunn E. Combination therapy with gold and hydroxychiorquine in rheumatoid arthritis: a prospective, randomized, placebo-controlled study, Br J Rheumatol 1989; 28:128-133.

21. Genovese MC, Cohen S, Moveland L. For 20000223 Study group. Combination therapy with etanercept and anakinra in RA who have seen treated unsuccessfully with MTX. Arthritis Rheum 2004; 50:1412-9.

22. Kievit W, Fransen J, visser H. Long term effectiveness & safety of TNF-□ blocking agents in daily clinical practice: results from Dutch Rheumatoid Arthritis monitoring register. Rheumatology (Oxford) 2011; 50: 196-203.

23. Singh JA, Christensen R, Well GA. Adverse effects of biologicals: a network meta-analysis and Cochrane overview. Cochrane Data Base Syst Rev 2010; 10: CD 008794.

24. BMJ 2011; 343: d4027, d0i: 10.1136/bmJ. d 4027.

25. Fransen J, van Riel P.L.C.M.The disease activity score and the EULAR response criteria. Clin Exp Rheumatol 2005; 23 (suppl39):593-9.

26. Felson DT, Anderson JJ, Boers M, Et al. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 38; 727-35.

27. Maxwell L,Sing JA. Abatacept for rheumatoid arthritis.Cocrane Database Syst Rev 2009; 4: CD 007277.

28. Mertens M, Singh JA. Anakinra for RA. Cochrane Database Syst Rev 2009; 1: CD 005121.

29. Solomon DH, Avom J, Katz JN, Weinblatt ME, Setoguchi S, Levin R, Schneeweiss S,.Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum 2006; 54:3790-8. Krishnan E, Fries JF, Reduction in long term Functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med 2003; 115:371-6.