WW Med 2019 Vol:1 Issue:6 184-191

Worldwide Medicine

Review

Biological treatment for rheumatoid arthritis: a review of the main approved monoclonal antibodies

José Hidalgan Galdino Faustino[1], Douglas Henrique de Oliveira[1], Thais Cristina Casimiro Fernandes[2], Patricia Ucelli Simioni[3]

[1]*Bachelor's in biomedical science Faculdade de Americana, FAM.*

[2]*PhD in Cellular and Molecular Biology, Faculdade de Americana, FAM.*

[3]*PhD in Immunology, Faculdade de Americana, FAM.*

Received: 21 June 2019 / Accepted: 25 July 2019

Abstract

Rheumatoid arthritis (RA) is a condition that affects mobility and the quality of life of the patient by affecting small and large joints and other organs. Its etiology is unknown, and its main characteristic is bone erosion and synovial inflammation. The conventional treatments involve the use of corticosteroids, immunosuppressants and anti-inflammatory drugs. A very effective new therapeutic option is the biological therapy with monoclonal antibodies. The monoclonal antibody therapy is highly specific but also with side effects. The present work details the application of biological therapies based on monoclonal antibodies for the treatment of RA patients. In this sense, cytokine-drive monoclonal antibodies may control or inhibit the immune response in RA. This therapeutic possibility has as a response the reduction of structural and joint damage.

Keywords: Arthritis, therapy, antibody, monoclonal, biological, cytokine.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that has a high destructive potential throughout its progression. The disease evolution generates significant social and economic costs. [1–3] This is a multifactorial and systemic disease of unknown etiology, which can mainly affect the joints, evolving with joint destruction and deformity, often becoming incapacitating. [4,5]

Corresponding Author: Patricia Ucelli Simioni, Rua Joaquim Boer,733 Americana, SP Brazil 13477-360 Tel: +5519996991899 E-mail: patriciasimioni@fam.br
DOI: 10.5455/ww.53482

The most common clinical manifestation of rheumatoid arthritis is pain and diffuse and symmetrical joint edema, with preferential involvement of small peripheral joints and with stiffness surges of variable duration. The onset of the disease is usually insidious, occurring in approximately a few weeks. Sometimes there is a time interval between the onset of symptoms until systemic arthritis is characterized, which arises with the progression of the disease. Conventional corticosteroid and immunosuppressive therapies are the first line of treatment for patients, and these drugs can have several adverse effects, including alterations in the body development, immunosuppression, and recurrent infections. However, with continual use these drugs may lose their clinical efficacy. [1,2,6–9]

It is estimated that RA affects 2 million people in Brazil. Once a patient is diagnosed with the disease, treatment with conventional drugs such as methotrexate, an immunomodulator and a first-line drug, is followed by immunosuppressants and corticosteroids, but these drugs have many side effects. Some patient can present high number of infections, gastrointestinal alterations, anemias, dermatitis among others. [1,2,10]

The biological therapy is a new therapeutic option since monoclonal antibodies can block proinflammatory cytokines by inhibiting its response. Researches showed greater efficacy and less adverse effects of this treatment compared to conventional, highlighting the efficacy of this therapy in patients with Rheumatoid Arthritis. [11–13]

The objective of the research was to present a review of the literature presenting the treatment with monoclonal antibodies as a therapeutic option for patients with rheumatoid arthritis.

Methods

The present review was conducted by a bibliographical survey of studies published in scientific articles and journals, both national and international, available on the subject in the PubMed and Scielo indexes, using the descriptors: rheumatoid arthritis, biological therapy and monoclonal antibodies. which located 143 articles. A total of 104 studies related to the following exclusion criteria were excluded: studies with conventional drugs, diagnostic, related diseases. The timeline for inclusion of articles was from 2010 to 2018.

Development

Rheumatoid arthritis has an unknown etiology and is characterized by several symptoms such as: symmetrical peripheral polyarthritis, which can lead to deformity and joint destruction, due to erosion of the bone and cartilage. It affects more women than men, and its incidence increases with age. It usually affects large and small joints in association with various manifestations, such as morning stiffness, fatigue and weight loss. When it involves other organs, the morbidity and severity of the disease are higher, which can reduce life expectancy in five to ten years. With the progression of the disease, patients begin to be unable to perform physical activities, routine daily and professional activities [14,15.]

Radiological changes of joint structures can be observed in the first two years of the disease. After 5 to 10 years of its onset, some of the patients' present deterioration of functional status, progressive incapacity to work and evolution of radiological lesions. Premature death may occur from both the disease itself and from the comorbidities. These evidences have changed the traditional view of the prognosis of rheumatoid arthritis, proposing that a more aggressive treatment may be more coherent with the evolution observed in the medium and long term. In this sense, new therapeutic options have emerged and promise to revolutionize the treatment of patients with rheumatoid arthritis [2,7,10,13.]

Conventional Treatments

Rheumatoid arthritis (RA) treatment includes drug and physical therapy, psychosocial support and surgical approaches. Drug therapies include the use of non-hormonal anti-inflammatory drugs (NSAIDs), corticosteroids, synthetic and biological disease course modifying drugs (DMARDs) and immunosuppressive drugs. Conventional treatments include

the use of immunosuppressive drugs and the most commonly used are non-steroidal anti-inflammatory drugs, corticosteroids, and the association of disease-modifying drugs (chloroquine/hydroxychloroquine, sulfasalazine, methotrexate), preferably up to three months after the onset of the disease. In those patients with worse prognosis, the use of methotrexate and immunosuppressants is recommended. [3,16,17]

It is well established that patients treated with disease-modifying drugs (DMARD), even in the first weeks of illness, evolve better than those who started treatment later. The "window of opportunity" concept emphasizes the need for the immediate use of DMARDs, associated or not to corticosteroids, aiming at the early control of the intra-articular inflammatory process, prevention of pannus formation and destruction of the affected joint.[10,14,16,18,19] Table 1 shows some of the drugs modifying the course of the disease, the mean time to action, the usual dose and the ways of monitoring the disease.

Table 1. Immunosuppressive drugs and synthetic drugs modifying the course of arthritis, mean time of action, usual dose and forms of disease monitoring[10,16.]

Disease-modifying drugs (DMARD)	**Average time to action**	**Usual dose**	**Monitoring**
Methotrexate	1-3 months	10-30 mg/week	Complete blood count, liver tests, creatinine.
Sulfasfazine	1-3 months	1-3g/day	Complete blood count, CAD hepatic tests
Leflunomide	1-2 months	20 mg/day	Complete blood count, liver tests, creatinine
Hydroxychloroquine sulphate	3-6 months	6mg/kg/day	Eye examination and leukogram
Chloroquine diphosphate	3-6 months	4mg/kg/day	Eye examination and leukogram
Salts of gold (aurothioglycoside or sodium aureotiomalate)	Not available	25-50mg/week	Complete blood count, liver tests, creatinine
Immunosuppressive drugs	**Average time to action**	**Usual dose**	**Monitoring**
Azathioprine	2-3 months	1-3 mg/kg/day	Complete blood count, liver tests
Cyclophosphamide	2-4 months	2-2.5 mg/kg/ day	Complete blood count, blood pressure and renal function
Cyclosporine	2-4 months	3-5 mg/kg/day	Blood pressure and renal function

Brazilian Rheumatology Consensus at 2012 indicates that immediately after the diagnosis, the rheumatologist must prescribe a drug modifying the course of the disease (DMCD), being methotrexate the drug of choice. If there is no adequate response after the use of two synthetic DMARD schemes, they should be evaluated for biological DMARDs, with the recommendation of the use of anti-TNF agents as the initial biological therapy. Only after therapeutic failure to a first biological DMARD, other biologicals could be used. Exceptionally, biological DMARDs may be considered earlier [16.]

Methotrexate (MTX) is an immunomodulatory agent whose action consists in inhibiting the synthesis of DNA, RNA, thymidine and proteins. The anti-inflammatory effects of MTX in RA appear to be related, at least in part, to the modulation of adenosine metabolism and to the possible effects on tumor necrosis factor (TNF) pathways. The immunosuppressive and toxic effects of MTX are due to inhibition of the dihydrofolate reductase, an enzyme involved in folic acid metabolism, which avoids the reduction of the dihydrofolate to active tetrahydrofolate. The maximum concentration occurs 1-5 hours after oral administration (VO) and 30-60 minutes intramuscular (IM) or subcutaneous (SC) administration [3,20,21.]

In some patients with indication of surgical treatment there is a synovectomy for persistent synovitis and resistant to conservative treatment, arthrodesis, total arthroplasties, among others [15,22.]

Monoclonal antibodies in rheumatoid arthritis

Currently there are seven classes of biologics available or under evaluation for the treatment of rheumatoid arthritis, including TNF inhibitors or blocker (infliximab, adalimumab, etanercept, golimumab and certolizumab pegol); inhibitors of Interleukin-6 (IL-6) (tocilizumab); inhibitors of Interleukin-12/23 (IL23) (ustekinumab); inhibitors of Interleukin-17 (IL-17) (secukinumab); inhibitors of B-cell (anti-CD20, rituximab); antagonists of Interleukin-1 (IL-1) receptor (anakinra); and inhibitors of T-cell costimulation (anti-CTLA-4, abatacept).[23] This review will focus only on the monoclonal antibodies approved for treatment of rheumatoid arthritis (Table 2).

Table 2. Monoclonal antibodies approved by the FDA for therapeutic treatment for rheumatoid arthritis.[16,23–27]

Antibody	Route	Type	Target
Adalimumab	subcutaneous	fully human	TNF
Certolizumab pegol	subcutaneous	Fab fragment humanized	TNF
Golimumab	subcutaneous	fully human	TNF
Infliximab	intravenous	chimeric, biosimilar	TNF
Sarilumab	subcutaneous	fully human	IL6R
Tocilizumab	intravenous	humanized	IL6R

Monoclonal antibodies, as a target therapy, have high specificity with few side effects and are the focus of many researches. [16,23–27] In the early 1980s, it was already known that in the synovial membrane of RA patients there was often a high expression of several cytokines implicated in immune-inflammatory reactions. Therefore, at the end of the decade and beginning of the 1990s, TNF was shown to be an ideal target for the eventual control of joint inflammation. [28,29]

Anti-TNF monoclonal antibodies

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory agent produced by macrophages and T cells and associated with destruction of the joints and synovitis in RA. There are two cell surface TNF receptors (TNFRs), which mediate TNF activity in effector cells. There are also soluble TNF receptors that act as regulators of the inflammatory response by inhibiting TNF activity. [23,27]

TNF-α blockers have been shown to be quite effective in RA patients and include infliximab, a chimeric anti-TNF monoclonal antibody; etanercept, a soluble TNF receptor and; adalimumab, a fully humanized anti-TNF monoclonal antibody. These TNF-α blockers, when used as monotherapy, are as effective as methotrexate in reducing disease activity,

as well as slowing the onset of erosions. However, their efficacy is increased when they are used in combination with methotrexate.[23,27,30–32]

Among TNF blockers, adalimumab is a monoclonal antibody that contains only human peptide sequences against the TNF-α molecule. It especially neutralizes biological function of TNF-α and blocks its interaction with receptors p55 and p75 of TNF on the cell surface. As with infliximab, adalimumab binds to soluble and membrane-bound TNF-α and may cause lysis of TNF-α-expressing cells on its surface.[29,33–35] Infliximab (IFX) is a human-murine chimeric anti-TNF monoclonal antibody that binds with high affinity to soluble and transmembrane forms of TNFα. Since infliximab is also composed of a murine protein, adverse effects during the infusion period are frequent, including anaphylactic reaction [12,30,32,36]

In general, TNF blockers are contraindicated in pregnant or lactating women, in patients with congestive heart failure, during active infection, and in cases of high risk for the development of infections or recurrent lung infections, as well as in patients with congestive heart failure. patients with multiple sclerosis or current or past malignant tumors. Due to the high prevalence of tuberculosis and reports of reactivation of tuberculosis with the use of blockers, these agents should be used with extreme caution in patients with susceptibility or previous history of tuberculosis. The main adverse effects related to treatment with TNF-α inhibitors are infections (mainly tuberculosis), autoimmune diseases, demyelinating diseases, neoplasms (lymphoma) and congestive heart failure.[23,30,33]

Anti -IL6 receptor monoclonal antibodies

Interleukin-6 (IL-6) is a proinflammatory and immunoregulatory cytokine that helps in host defense against tissue injuries. IL-6 is relevant in systemic inflammatory symptoms since it induces acute phase protein expression, such as fibrinogen, hepcidin and C-reactive protein.[37]

Since up to one third of RA patients did not response to anti-TNF therapy, agents targeting IL-6 are promising agents in RA treatment. Anti-IL-6 monoclonal antibodies to rheumatoid arthritis include receptor blockers such as sarilumab, which was approved in 2017.[32] Tocilizumab, an anti- IL-6 receptor monoclonal antibody, as a potent new therapeutic agent in RA treatment specifically in failing of anti-TNF therapy.[38]

Sarilumab and tocilizumab can generate neutropenia, dyslipidemia, injection site reactions, and gastrointestinal perforation. Sarilumab is an alternative to patients with RA who have not responded to prior tumor necrosis factor-α inhibitors or synthetic DMARDs.[39]

Conclusions

At present, treatment of patients with rheumatoid arthritis involves the early use of disease modifying drugs (MMCD) that prevent damage and preserve joint integrity and functionality. The introduction of biological agents allowed a faster and better treatment on the pathophysiological aspects of RA. The new agents have a rapid onset of action, sustained response and acceptable tolerability. Numerous studies have demonstrated the clinical efficacy and safety of TNF-α and Il-6R blockers in the control of RA signs and symptoms, with a significant contribution to the prevention and reduction of disease progression. Some other monoclonal antibodies, such as ustekinumab or guselkumab did not presented effective effect for the treatment of RA patients.

Conflicts of interest:

There are no conflicts of interest.

References

1. Almeida M do STM, Almeida JVM, Bertolo MB. Características demográficas e clínicas de pacientes com artrite reumatoide no Piauí, Brasil – avaliação de 98 pacientes. Rev Bras Reumatol. 2014;54(5):360–5.

2. Maria L, Cruz BA, Brenol CV, Pereira IA, Rezende-fronza LS, Bertolo MB, et al. Reumatologia para o tratamento da artrite reumatoide. Rev Bras Reumatol [Internet]. 2012;52(2):152–74.

3. Henrique da Mota LM, Afonso Cruz B, Viegas Brenol C, Alves Pereira I, Rezende-Fronza LS, Barros Bertolo M, et al. Diretrizes para o tratamento da artrite reumatoide. Rev Bras Reumatol [Internet]. 2013;53(2):158–83.

4. Torigoe D, Reumatol IL-RB, 2006 undefined. Artrite reumatóide e doenças cardiovasculares. SciELO Bras [Internet]. [cited 2018 Aug 23];

5. Plum SM, Park EJ, Strawn SJ, Moore EG, Sidor CF, Fogler WE. Disease modifying and antiangiogenic activity of 2-Methoxyestradiol in a murine model of rheumatoid arthritis. BMC Musculoskelet Disord. 2009 Dec 1 [cited 2018 Aug 23];10(1):46.

6. Laurindo IMM, Ximenes AC, Lima FAC, Pinheiro GRC, Batistella LR, Bertolo MB, et al. Artrite reumatóide: Diagnóstico e Tratamento. Rev Bras Reumatol. 2004;44(6):435–42.

7. da Mota LMH, dos Santos Neto LL, Burlingame RW, Ménard HA, Pereira IA, de Carvalho JF, et al. Incapacitação e qualidade de vida não são influenciadas pela prevalência de autoanticorpos em pacientes com artrite reumatoide inicial - resultados da Coorte Brasília. Rev Bras Reumatol. 2012;52(6):824–9.

8. Carvalho A, Maximiano S, Albuquerque C, Mota S, Kozak C. Uso de corticoterapia e Infliximabe para tratamento de pioderma gangrenoso em paciente com artrite reumatoide. Rev Bras Reumatol. 2017;57:S42.

9. de Carvalho MMN, Novaes AE, de Carvalho EM, Araújo MI. Doenças reumáticas auto-imunes em indivíduos infectados pelo HTLV-1. Vol. 46, Revista Brasileira de Reumatologia. 2006. p. 334–9.

10. Brenol CV, Mota, Licia Maria Henrique da, Cruz BA, Pileggi GS, Pereira IA, Rezende LS, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia sobre vacina{ç}{ã}o em pacientes com artrite reumatoide. Rev Bras Reumatol. 2013;53(1):13–23.

11. Faleiro L, Araújo L, Saúde MV-SCB e da. A terapia anti-TNF-a na artrite reumatóide. uel.br. [cited 2018 Aug 23];

12. Barbosa CMPL, Terreri MTRA, Oliveira SKF, Rodrigues MCF, Bica BERG, Sacchetti S, et al. Efeitos adversos durante a infusão de infliximabe em crianças e adolescentes - Estudo multicêntrico. Rev Bras Reumatol [Internet]. 2008 Oct [cited 2018 Aug 23];48(5):278–82.

13. Sociedade Portuguesa de Reumatologia. Artrite Reumatóide. Soc Port Reumatol [Internet]. 2013;1–24.

14. Laurindo I, Ximenes A, … FL-RB, 2004 undefined, Reumatologia FL-… de, 2004 undefined, et al. Artrite reumatóide: diagnóstico e tratamento. SciELO Bras [Internet]. [cited 2018 Aug 23];

15. David JM, Mattei RA, Mauad JL, Almeida, Lauren Gabrielle de Nogueira MA, Menolli PV da S, Menolli RA. Estudo clínico e laboratorial de pacientes com artrite reumatoide diagnosticados em serviços de reumatologia em Cascavel, PR, Brasil. Rev Bras Reumatol. 2013;53(1):61–5.

16. Mota LMH da, Cruz BA, Brenol C V, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia para o tratamento da artrite reumatoide. Rev Bras Reumatol [Internet]. 2012 [cited 2018 Aug 23];52(2):135–74.

17. Sandborn WJ, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: a review of agents, pharmacology, clinical results, and safety. Inflamm Bowel Dis [Internet]. 1999 May [cited 2014 Dec 12];5(2):119–33.

18. Bértolo MB, Brenol CV, Schainberg CG, Neubarth F, de Lima FAC, Laurindo IM, et al. Atualização do consenso Brasileiro no diagnóstico e tratamento da artrite reumatóide. Rev Bras Reumatol. 2007;47(3):151–9.

19. Mota LMH da, Laurindo IMM, Santos Neto LL dos. Artrite reumatoide inicial: conceitos. Rev Assoc Med Bras

[Internet]. 2010 [cited 2018 Aug 30];56(2):227–9.

20. Mota LM., Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. 2012 Brazilian Society of Rheumatology consensus for the treatment of rheumatoid arthritis [Internet]. Vol. 52, Revista Brasileira de Reumatologia. 2012 [cited 2018 Aug 23]. p. 135–74.

21. McDonald JWD, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane database Syst Rev [Internet]. 2014 Jan [cited 2015 Feb 11];8:CD003459.

22. Mota LMH da, Laurindo IMM, Santos Neto LL dos. Princípios gerais do tratamento da artrite reumatoide inicial. Rev Assoc Med Bras [Internet]. 2010 [cited 2018 Aug 23];56(3):360–2.

23. Luchetti MM, Benfaremo D, Gabrielli A. Biologics in Inflammatory and Immunomediated Arthritis. Curr Pharm Biotechnol [Internet]. 2018 Mar 12 [cited 2018 Aug 23];18(12):989–1007.

24. Davis JM, Matteson EL, American College of Rheumatology, European League Against Rheumatism. My Treatment Approach to Rheumatoid Arthritis. Mayo Clin Proc [Internet]. 2012 Jul [cited 2018 Aug 23];87(7):659–73.

25. Rinaudo-Gaujous M, Paul S, Tedesco ED, Genin C, Roblin X, Peyrin-Biroulet L. Review article: biosimilars are the next generation of drugs for liver and gastrointestinal diseases. Aliment Pharmacol Ther [Internet]. 2013 Oct [cited 2015 Feb 19];38(8):914–24.

26. Silva GD da, Andrade EIG, Cherchiglia ML, Almeida AM, Guerra Júnior AA, Acurcio F de A. [Profile of spending on the treatment of rheumatoid arthritis for patients of the Unified Health System in the state of Minas Gerais - 2008-2013]. Cien Saude Colet [Internet]. 2018 [cited 2018 Aug 23];23(4):1241–53.

27. Rossi D, Modena V, Sciascia S, Roccatello D. Rheumatoid arthritis: Biological therapy other than anti-TNF. Int Immunopharmacol [Internet]. 2015 Aug [cited 2018 Aug 23];27(2):185–8.

28. Scheinberg M. O infliximab no tratamento da artrite reumatóide: quando e como usar. Hosp Albert Einstein [Internet]. 2005 [cited 2018 Aug 23];1(1):138–40.

29. Scheinberg M, Golmia R, Rollo C. O uso de agentes biológicos no tratamento de artrite reumatóide TT - A review of biological agents use in the treatment of reumathoid arthritis. Rev Bras Med [Internet]. 2015 [cited 2018 Aug 23];72(9).

30. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol [Internet]. 2013 Mar [cited 2014 Dec 27];9(3):164–72.

31. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor α monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum [Internet]. 2009 Aug [cited 2018 Aug 23];60(8):2272–83.

32. Mahajan TD, Mikuls TR. Recent advances in the treatment of rheumatoid arthritis. Curr Opin Rheumatol [Internet]. 2018 Feb [cited 2018 Aug 23];30(3):1.

33. Manzano R. Estudo da toxicidade do adalimumabe (Humira®) intravítreo para a retina de coelhos. 2010 [cited 2018 Aug 23];

34. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. Arthritis Rheum [Internet]. 2003 Jan [cited 2018 Aug 23];48(1):35–45.

35. Burness CB, Keating GM. Adalimumab: a review of its use in the treatment of patients with ulcerative colitis. BioDrugs [Internet]. 2013 Jun [cited 2015 Feb 18];27(3):247–62.

36. Costa JD, Almeida AM, Guerra AA, Cherchiglia ML, Andrade EIG, Acurcio FD. Treatment of rheumatoid arthritis in the Brazilian Unified National Health System: expenditures on infliximab compared to synthetic disease-modifying

anti-rheumatic drugs, 2003-2006. Cad Saude Publica [Internet]. 2014 [cited 2018 Aug 23];30(2):283–95.

37. Tanaka T, Hishitani Y, Ogata A. Monoclonal antibodies in rheumatoid arthritis: comparative effectiveness of tocilizumab with tumor necrosis factor inhibitors. Biologics [Internet]. 2014 [cited 2018 Aug 30];8:141–53.

38. Woodrick R, Ruderman EM. Anti-interleukin-6 therapy in rheumatoid arthritis. Bull NYU Hosp Jt Dis [Internet]. 2010 [cited 2018 Aug 30];68(3):211–7.

39. Boyce EG, Rogan EL, Vyas D, Prasad N, Mai Y. Sarilumab: Review of a Second IL-6 Receptor Antagonist Indicated for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2018 Aug 26 [cited 2018 Aug 30];780–91.