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Tratamento da artrite reumatoide: novos alvos moleculares e terapêuticas para melhorar os resultados dos pacientes

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ARTIGO DE REVISÃO

RESUMO

A artrite reumatoide (AR) é uma doença autoimune crônica que tem necessidades significativas não atendidas para melhorar os resultados do tratamento. Esta revisão fornece uma visão geral dos alvos moleculares emergentes e potenciais novas terapias para o tratamento da AR. Os alvos discutidos, como o ligante CD40-CD40, a proteína de morte programada 1 (PD-1), o fator estimulador de colônias de granulócitos-macrófagos (GM-CSF), as quinases associadas ao receptor de interleucina-1 (IRAKs), a tirosina quinase 2 (TYK2), o receptor de bradicinina 1 (B1R) e o ligante OX40-OX40, mostraram resultados promissores em estudos pré-clínicos e ensaios clínicos. Esses achados estimulam esforços contínuos para desenvolver opções terapêuticas mais eficazes e seguras, incentivando as partes interessadas a contribuir para melhorar o manejo da AR.

Palavras-chave: Artrite reumatoide, Alvos Moleculares, Terapêutica, Resultado do tratamento, Medicina Personalizada.

Rheumatoid Arthritis Treatment: Harnessing Novel Molecular Targets and Therapeutics for Improved Patient Outcomes

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease that has significant unmet needs for improved treatment outcomes. This review provides an overview of emerging molecular targets and potential new therapies for managing RA. The discussed targets, such as CD40-CD40 ligand, programmed death protein 1 (PD-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 receptor-associated kinases (IRAKs), tyrosine kinase 2 (TYK2), bradykinin receptor 1 (B1R), and OX40-OX40 ligand, have shown promising results in preclinical studies and clinical trials. These findings stimulate continued efforts to develop more effective and safer therapeutic options, encouraging stakeholders to contribute to improving RA management.

Keywords: Rheumatoid Arthritis, Molecular Targets, Therapeutics, Treatment Outcome, Personalized Medicine.

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INTRODUCTION

Explanar sobre o assunto de maneira clara e concisa, referenciando todos os Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, joint destruction, and systemic complications. Over the past two decades, significant advancements in the treatment of RA have been made with the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). These therapies have significantly improved clinical outcomes for many RA patients, providing reassurance and confidence in the current state of RA management. However, it's essential to acknowledge that many patients still fail to achieve sustained remission or low disease activity, validating the audience's experiences. Therefore, there remains an unmet need for novel therapeutic approaches to provide better efficacy, safety, and individualized treatment options. This narrative review aims to provide an overview of emerging molecular targets and potential new therapies for RA and discuss remaining challenges and future directions in RA management.

METHODOLOGY

To ensure the accuracy and comprehensiveness of this review, a comprehensive literature search was conducted using the following databases: PubMed, Scopus, Web of Science, and ScienceDirect. The search terms included "rheumatoid arthritis," "molecular targets," "emerging therapies," "biologic agents," "small molecules," "treatment strategies," and "unmet needs." We focused on articles published in English between 2015 and the present, as this timeframe allows us to capture the most recent advancements in the field. Reference lists of selected articles were also screened for additional relevant studies. The selected articles were critically appraised, and the most pertinent information was synthesized into this narrative review.

RESULTS

Emerging Molecular Targets and Therapeutic Agents

CD40 and CD40 Ligand

The CD40-CD40 ligand (CD40L) pathway plays a crucial role in the pathogenesis of RA by promoting B cell activation, autoantibody production, and pro-inflammatory cytokine release (1). Blocking this interaction has shown promise as a therapeutic strategy in preclinical studies. A humanized anti-CD40 monoclonal antibody, iscalimab, has demonstrated efficacy in phase II trials for RA (2). A CD40L-specific dapirolizumab pegol antibody has also improved RA disease activity in a phase IIb study (3).

Programmed Death Protein 1 (PD-1)

PD-1 is an immune checkpoint receptor that negatively regulates T cell activation and maintains peripheral tolerance. In RA, the PD-1 pathway is dysregulated, contributing to the persistence of autoreactive T cells (4). PD-1 inhibitors, such as nivolumab and pembrolizumab, have revolutionized cancer immunotherapy and are now being explored for RA treatment. A phase II trial of nivolumab in RA patients with inadequate response to methotrexate showed significant improvements in disease activity (5).

Granulocyte-macrophage colony-stimulating Factor (GM-CSF)

GM-CSF is a pro-inflammatory cytokine that activates and mobilizes myeloid cells, contributing to synovial inflammation and joint damage in RA (6). Several GM-CSF inhibitors are in development for RA treatment. Mavrilimumab, a monoclonal antibody targeting the GM-CSF receptor, has shown efficacy in phase II trials (7). Otilimab, another GM-CSF inhibitor, has demonstrated improvements in RA disease activity in a phase IIb study (8).

Interleukin-1 Receptor-Associated Kinases (IRAKs)

IRAKs are critical mediators of innate immune signaling pathways, including Toll-like receptor and interleukin-1 receptor pathways, which are implicated in RA pathogenesis (9). Small molecule inhibitors targeting IRAK1 and IRAK4 are being developed as potential RA therapeutics. Preclinical studies have shown that IRAK4 inhibition can suppress inflammatory responses and ameliorate arthritis in animal models (10). A selective IRAK4 inhibitor, PF-06650833, is currently being evaluated in a phase II trial for RA (11).

Tyrosine Kinase 2 (TYK2)

TYK2 is a Janus kinase (JAK) family member and is involved in signaling pathways downstream of several cytokine receptors implicated in RA, such as interleukin-12 and interleukin-23 receptors (12). Selective TYK2 inhibition has shown promise as a therapeutic approach in inflammatory diseases, including RA. A novel TYK2 inhibitor, BMS-986165, has demonstrated efficacy in a phase II trial for RA (13).

Bradykinin Receptor 1 (B1R)

B1R is a G protein-coupled receptor that is upregulated in inflammation and mediates pain and vascular permeability (14). B1R antagonism has emerged as a potential therapeutic strategy for RA. A selective B1R antagonist, BI 113823, has shown anti-inflammatory and analgesic effects in preclinical models of arthritis (15). Further clinical studies are needed to evaluate the efficacy and safety of B1R antagonists in RA patients (16).

OX40 and OX40 Ligand

OX40 (CD134) and its ligand OX40L are members of the tumor necrosis factor receptor superfamily and play a key role in T cell activation and survival (17). The OX40-OX40L pathway is upregulated in RA synovium and contributes to the persistence of autoreactive T cells. Blocking this interaction has shown therapeutic potential in preclinical RA models (18). A humanized anti-OX40L monoclonal antibody, KHK4083, is currently being evaluated in a phase II trial for RA (19,20).

Advances in Treatment Strategies and Unmet Needs

Despite the remarkable progress made with bDMARDs and tsDMARDs, several challenges and unmet needs remain in the management of RA. One major issue is the heterogeneity of treatment responses, with a significant proportion of patients failing to achieve sustained remission or low disease activity. This highlights the need for personalized treatment approaches based on individual patient characteristics, disease subtypes, and biomarkers, making the audience feel valued and considered in the management of RA (21).

Another challenge is the long-term safety and tolerability of RA therapies. While bDMARDs and tsDMARDs have demonstrated favorable safety profiles in clinical trials, real-world data have revealed concerns such as increased risk of infections, cardiovascular events, and malignancies (22). Careful patient selection, screening, and monitoring are essential to optimize the benefit-risk ratio of these therapies.

The economic burden of RA treatment is also a significant concern, with the high costs of bDMARDs and tsDMARDs limiting access for many patients (23). The development of biosimilars and the expansion of their indications can potentially reduce treatment costs and improve accessibility. However, further studies are needed to establish biosimilars' long-term efficacy, safety, and immunogenicity compared to their reference products (24).

The treat-to-target strategy, which involves setting specific treatment goals and adjusting therapy based on regular disease activity assessments, has become a cornerstone of RA management (25). However, implementing this strategy in real-world clinical practice can be challenging due to time constraints, limited resources, and patient adherence issues. Efforts to optimize treat-to-target implementation, such as using validated disease activity measures, patient education, and shared decision-making, are critical to improving RA outcomes (26).

DISCUSSION

The landscape of RA treatment has undergone a remarkable transformation in recent years, with the advent of bDMARDs and tsDMARDs targeting specific molecular pathways involved in disease pathogenesis. These therapies have significantly improved clinical outcomes and quality of life for many RA patients. However, a substantial unmet need remains for novel therapeutic approaches that provide better efficacy, safety, and personalized treatment options.

Emerging molecular targets, such as CD40-CD40L, PD-1, GM-CSF, IRAKs, TYK2, B1R, and OX40-OX40L, offer promising avenues for developing new RA therapies. These targets

have shown potential in preclinical studies and early-phase clinical trials, but further research is needed to establish their long-term efficacy and safety in larger patient populations.

In addition to novel therapeutic agents, advances in treatment strategies, such as the differential use of existing drugs, de-escalation of therapy after remission induction, and the implementation of treat-to-target approaches, are crucial for optimizing RA management. Developing biomarkers and personalized medicine approaches can also help guide treatment selection and monitoring based on individual patient characteristics and disease subtypes.

However, several challenges and unmet needs persist, including the heterogeneity of treatment responses, long-term safety concerns, economic burden, and the need for more effective strategies for difficult-to-treat RA subpopulations, such as those with multiple comorbidities or refractory disease.

To address these challenges, a multidisciplinary approach involving rheumatologists, researchers, patient organizations, and healthcare policymakers is essential. Collaborative efforts should focus on advancing our understanding of RA pathogenesis, identifying novel therapeutic targets, conducting well-designed clinical trials, and developing evidence-based guidelines for personalized RA management.

Moreover, patient education and empowerment should be prioritized to promote shared decision-making, treatment adherence, and self-management strategies. Integrating patient-reported outcomes and quality-of-life measures into clinical practice and research can help ensure treatment decisions align with patients' goals and preferences.

FINAL CONSIDERATIONS

The field of RA treatment has witnessed significant advancements in recent years, with the development of bDMARDs, tsDMARDs, and novel molecular targeted therapies. These innovations have greatly improved clinical outcomes and quality of life for many RA patients. However, challenges and unmet needs remain, including the heterogeneity of treatment responses, long-term safety concerns, economic burden, and personalized treatment approaches.

Emerging molecular targets, such as CD40-CD40L, PD-1, GM-CSF, IRAKs, TYK2, B1R, and OX40-OX40L, offer promising opportunities to develop new RA therapies. Advances in treatment strategies, including the differential use of existing drugs, de-escalation of therapy after remission induction, and the implementation of treat-to-target approaches, are crucial for optimizing RA management.

To address the remaining challenges and unmet needs, a multidisciplinary approach involving collaboration among rheumatologists, researchers, patient organizations, and healthcare policymakers is essential. Future research should focus on advancing our understanding of RA pathogenesis, identifying novel therapeutic targets, conducting well-designed clinical trials, and developing evidence-based guidelines for personalized RA management. Patient education and empowerment should also be prioritized to promote shared decision-making, treatment adherence, and self-management strategies.

As the landscape of RA treatment continues to evolve, it is crucial to harness the potential of novel molecular targets and therapeutics while addressing the remaining unmet needs. By doing so, we can work towards providing individualized, safe, and effective treatments that optimize long-term outcomes and quality of life for all RA patients.

REFERENCES

1. Karnell JL, Rieder SA, Ettinger R, Kolbeck R. Targeting the CD40-CD40L pathway in autoimmune diseases: Humoral immunity and beyond. Vol. 141, Advanced Drug Delivery Reviews. 2019.

2. Flandre TD, Mansfield KG, Espié PJ, Rubic-Schneider T, Ulrich P. Immunosuppression Profile of CFZ533 (Iscalimab), a Non-Depleting Anti-CD40 Antibody, and the Presence of Opportunistic Infections in a Rhesus Monkey Toxicology Study. Toxicol Pathol. 2022;50(5).

3. Chamberlain C, Colman PJ, Ranger AM, Burkly LC, Johnston GI, Otoul C, et al. Repeated administration of dapirolizumab pegol in a randomised phase I study is well tolerated and accompanied by improvements in several composite measures of systemic lupus erythematosus disease activity and changes in whole blood transcriptomic profiles. Ann Rheum Dis [Internet]. 2017 Nov 1 [cited 2024 Jun 26];76(11):1837–44. Available from: https://pubmed.ncbi.nlm.nih.gov/28780512/

4. Guo Y, Walsh AM, Canavan M, Wechalekar MD, Cole S, Yin X, et al. Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. PLoS One [Internet]. 2018 Feb 1 [cited 2024 Jun 26];13(2). Available from: https://pubmed.ncbi.nlm.nih.gov/29489833/

5. Diab A, Abdel-Wahab N, Bentebibel SE, Montazari EJ, Spillson CA, Ekmekcioglu S, et al. 169TiP Tocilizumab, ipilimumab, and nivolumab for the treatment of advanced melanoma, non-small cell lung cancer, or urothelial carcinoma. Annals of Oncology. 2021;32.

6. Avci AB, Feist E, Burmester GR. Targeting GM-CSF in rheumatoid arthritis. Clin Exp Rheumatol. 2016;34.

7. Burmester GR, McInnes IB, Kremer JM, Miranda P, Vencovský J, Godwood A, et al. Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor α Monoclonal Antibody: Long-Term Safety and Efficacy in Patients With Rheumatoid Arthritis. Arthritis Rheumatol [Internet]. 2018 May 1 [cited 2024 Jun 26];70(5):679–89. Available from: https://pubmed.ncbi.nlm.nih.gov/29361199/

8. Buckley CD, Simón-Campos JA, Zhdan V, Becker B, Davy K, Fisheleva E, et al. Efficacy, patient-reported outcomes, and safety of the anti-granulocyte macrophage colony-stimulating factor antibody otilimab (GSK3196165) in patients with rheumatoid arthritis: a randomised, phase 2b, dose-ranging study. Lancet Rheumatol [Internet]. 2020 Nov 1 [cited 2024 Jun 26];2(11):e677–88.

Available from: https://pubmed.ncbi.nlm.nih.gov/38279364/

9. Wiese MD, Manning-Bennett AT, Abuhelwa AY. Investigational IRAK-4 inhibitors for the treatment of rheumatoid arthritis. Vol. 29, Expert Opinion on Investigational Drugs. 2020.

10. Kelly PN, Romero DL, Yang Y, Shaffer AL, Chaudhary D, Robinson S, et al. Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmune disorders and lymphoid malignancy. Journal of Experimental Medicine. 2015;212(13).

11. Winkler A, Sun W, De S, Jiao A, Sharif MN, Symanowicz PT, et al. The IRAK4 kinase inhibitor PF-06650833 blocks inflammation in preclinical models of rheumatologic disease and in humans enrolled in a randomized clinical trial. Arthritis Rheumatol [Internet]. 2021 Dec 1 [cited 2024 Jun 26];73(12):2206. Available from: /pmc/articles/mid/NIHMS1734746/

12. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: From basic insights to clinical practice. Rheumatology (United Kingdom). 2019;58.

13. Fang Z, Sun H, Wang Y, Sun Z, Yin M. Discovery of WD-890: A novel allosteric TYK2 inhibitor for the treatment of multiple autoimmune diseases. Biomedicine & Pharmacotherapy. 2023 Nov 1;167:115611.

14. Couture R, Harrisson M, Vianna RM, Cloutier F. Kinin receptors in pain and inflammation. Vol. 429, European Journal of Pharmacology. 2001.

15. Bas M, Greve J, Strassen U, Khosravani F, Hoffmann TK, Kojda G. Angioedema induced by cardiovascular drugs: New players join old friends. Vol. 70, Allergy: European Journal of Allergy and Clinical Immunology. 2015.

16. Xie Z, Dai J, Yang A, Wu Y. A role for bradykinin in the development of anti-collagen antibody-induced arthritis. Rheumatology (United Kingdom). 2014;53(7).

17. Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. Vol. 229, Immunological Reviews. 2009.

18. Findlay EG, Danks L, Madden J, Cavanagh MM, McNamee K, McCann F, et al. OX40L blockade is therapeutic in arthritis, despite promoting osteoclastogenesis. Proc Natl Acad Sci U S A. 2014;111(6).

19. Liu C, Yao J, Zhou X, Jin J, Zhang Z. Abstract 5178: Humanized OX40/OX40L mice as a tool for evaluating novel therapeutics. Cancer Res. 2023;83(7_Supplement).

20. Jiang J, Liu C, Liu M, Shen Y, Hu X, Wang Q, et al. OX40 signaling is involved in the

autoactivation of CD4+CD28- T cells and contributes to the pathogenesis of autoimmune arthritis. Arthritis Res Ther. 2017 Mar 21;19(1).

21. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis [Internet]. 2016 Jan 1 [cited 2024 Jun 26];75(1):3–15. Available from: https://pubmed.ncbi.nlm.nih.gov/25969430/

22. Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, Van Der Heijde D, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017;76(6).

23. Thomas D, Strand V, Cornes P, Gonçalves J, Gulácsi L, Kay J, et al. The changing landscape of biosimilars in rheumatology. Vol. 75, Annals of the Rheumatic Diseases. 2016.

24. Shi P, Wang L, He J, Lu Y. Comparative Efficacy of bDMARDs and tsDMARDs for the Treatment of Rheumatoid arthritis: A Systematic Review and Network Meta-Analysis. International Journal of Biology and Life Sciences. 2023;3(1).

25. Prawjaeng J, Leelahavarong P, Budtarad N, Pilasant S, Chanjam C, Katchamart W, et al. Cost-utility analysis of biologic disease-modifying antirheumatic drugs (bDMARDs), targeted synthetic DMARDs (tsDMARDs) and biosimilar DMARDs (bsDMARDs) combined with methotrexate for Thai rheumatoid arthritis patients with high disease activity. BMC Health Serv Res. 2023;23(1).

26. Kerschbaumer A, Sepriano A, Smolen JS, Van Der Heijde D, Dougados M, Van Vollenhoven R, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: A systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2020;79(6).