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Efficacy of Vitamin D versus Biological Agents in the Management of Rheumatoid Arthritis

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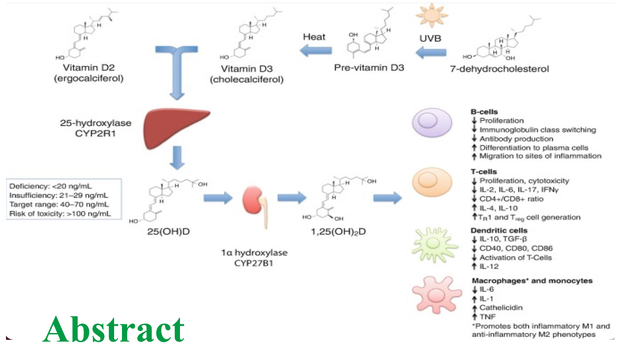


Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease leading to joint destruction. There are several treatment options available to patients, including conventional disease modifying antirheumatic drugs (DMARDS) and biological agents, but their efficacies vary per patient and tote significant adverse effects and cost. There is, however, encouraging evidence to suggest the incorporation of vitamin D in treatment regimens may be a promising option for patients. A comprehensive literature review was conducted using PubMed and CINHAL databases, employing keywords and MeSH terms related to RA treatment options, with the goal to compare efficacy of biological agents and vitamin D in the symptom management and progression of RA. Eleven studies met criteria and were analyzed. These studies evaluated vitamin D, tumor necrosis factors, interleukin inhibitors, B-cell inhibitors, and T-cell inhibitors in the treatment and prevention of RA progression. The review highlights the complexity of managing RA and underscores the favorable outcomes observed in symptom management and disease progression by biological agents compared to vitamin D. Although vitamin D demonstrates promise as an adjunctive and potential preventative therapy, further research that includes vitamin D as part of a treatment regimen with biologics is necessary to evaluate its potential and proper use in the treatment of RA. Providers must remain informed about optimal practice recommendations, be amenable to a trial-and-error approach to treatment, and consider combination therapy, with use of DMARDS, biologics, and adjunctive therapies such as vitamin D to best meet the needs of individual patients.

Introduction

RA is a chronic autoimmune condition affecting synovial joints, which causes inflammatory arthritis and joint destruction. It may progress to affect the skin, heart, lungs, and eyes. Its progressive nature makes early diagnosis and treatment crucial for the longevity and functionality of patients.

RA has an incidence of 0.24 to 1 percent of the world population; it is twice as common in women than men, and has an even higher incidence in certain populations, such as the Pima Native Americans, with ten times the average incidence and prevalence. Other risk factors include smoking, obesity, and family history (England, B & Mikuls, T., 2023).

Conventional treatment includes disease modifying antirheumatic agents (DMARDS). Those with poor or inadequate treatment response to DMARDS may change or add on treatment with a biological agent (biologic). The main biologics available are those which inhibit: tumor necrosis factors, interleukins, T-cells, and B-cells. Both DMARDS and biologics are associated with high cost and risk of serious adverse effects, and their efficacy per patient varies tremendously. These challenges elicit the need for exploration of alternative and complementary therapeutic approaches, such as with vitamin D,

Vitamin D is a promising alternative therapy for those with RA. Vitamin D works on the immune system by inhibiting B cell proliferation, obstructs B cell differentiation, suppresses secretion of immunoglobulins, suppresses T cell proliferation, alters T cell maturation and in turn, reduces inflammatory cytokine proliferation and increasing anti-inflammatory cytokines. Therefore, vitamin D helps regulate the immune system and maintain homeostasis by preventing excess inflammation, positioning it as a compelling treatment option or supplement for those with RA. Although direct comparison of treatment with vitamin D versus biologics remains understudied, the exploration of the topic is essential to inform evidence-based treatment and improve patient outcomes in the management of RA.

Research Question

In adults with rheumatoid arthritis, does vitamin D or the use of biological agents have better efficacy for symptom management and/or slowing the progression of disease?

Literature Review

Vitamin D

- Buondonno et al. (2017) conducted a double-blind placebo-controlled trial which found that patients with early RA showed decreased 25OH-vitamin D levels (p=0.002) compared to controls and that adding vitamin D to standard RA treatment showed improved global health (p=0.045).
- Hahn et al. (2021) performed a randomized, double-blinded, placebo-controlled trial to assess the impact of vitamin D on autoimmune disease incidence. They found that over 5.3 years, those who received 2000 IU vitamin D daily had a 22% less incidence in autoimmune disease incidence compared to the placebo group. In the last three years of the study, those treated with vitamin D showed 39% fewer participants with autoimmune disease than the placebo group (p=0.005).
- Li et al. (2018) conducted a randomized, double-blinded, phase II clinical trial to compare the effect of two forms of vitamin D, calcitriol (1 alpha, 25-dihydroxy vitamin D), and 22-oxa-calcitriol, on RA. Both treatment groups showed decreased swollen joints, increased vitamin D levels, decreased CRP and ESR, reduced pain, and improvement in their Health Assessment Questionnaire Disease Activity Index compared to the placebo (p-values <0.0001). They found that calcitriol caused hypercalcemia, while 22-oxa-calcitriol did not (p<0.001).

TNF inhibitors

- Corrado et al. (2017) evaluated the impact of tumor necrosis factor-α inhibitors on disease activity and inflammatory anemia in RA patients. They compared three different TNF- α inhibitors (etanercept, adalimumab, or infliximab) and found that after three months, all three groups had decreased disease activity (DAS-28) scores (p=0.01). At 9 and 12 months, etanercept had superior outcomes than the other two in DAS28 scores (p<0.01 and p=0.04, respectively). They also found that treatment improved hemoglobin levels in all three groups at three months (p<0.05).
- Scott et al. (2014) conducted a 12-month open-label, randomized, multicenter trial to compare combination DMARD (cDMARD) treatment with treatment of TNF inhibitor (TNFi) plus methotrexate (MTX) or another DMARD. They found similar benefit of perceived symptom relief and management of symptoms with either group (p=0.317). Both groups had similar adverse effects and toxicities (p=0.110), as well as similar remission rates (p=0.085). However, the cost of cDMARD therapy was found to be lower than TNFi therapy, which should be considered.

Interleukin inhibitors

- Feist et al. (2022) studied whether the monoclonal antibody targeting the interleukin 6 (IL-6), olokizubmab (OKZ), was safe and efficacious in treating patients with RA who had inadequate response to treatment with TNFi. They found treatment with OKZ improved the American College of Rheumatology 20 (ACR20) response and Disease Activity Score 28 joint count based on CRP (DAS28-CRP) compared to the placebo (p<0.01). They found that the safety profile of OKZ was similar to that of other IL-6 inhibitors, making it a good option for patients who are not adequately controlled by TNFi therapy.
- Genovese et al. (2018) conducted a 12-week, randomized and double- blinded phase two clinical trial to assess the safety and efficacy of ABT-122, an immunoglobulin targeting both TNF and IL-17A in patients with RA and an inadequate response to MTX. The study showed dose-related increases in ACR20 response, but no significant changes elsewhere. This indicates that dual inhibition of TNF plus IL is as safe as but may not be more efficacious than TNF inhibition alone.

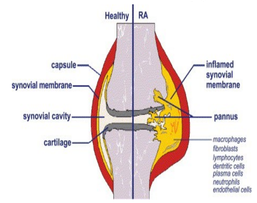
B-cell inhibitors

- Behrens et al. (2021) randomized, double-blinded, placebo-controlled phase 3 clinical trial assessed the efficacy and safety of the B-cell inhibitor, rituximab, plus leflunomine (LEF), a DMARD often used in those intolerant to MTX, versus LEF plus placebo. There was no statistically significant difference in the primary outcome, ACR50 (p=0.081), but they did see increased response to treatment in ACR20 at weeks 12, 16, and 24, in DAS28 from weeks 12-24 (p≤0.05), and those who achieved DAS28 remission at week 24 (p=0.004), suggesting potential benefit to adding rituximab to LEF therapy; however, close monitoring is required due to the large number of adverse effects reported.
- Porter et al. (2016) conducted an open-label, randomized, non-inferiority study to compare efficacy and cost-effectiveness of rituximab with that of TNFis in patients with an inadequate response to DMARDs. They found that rituximab was non-inferior to TNFis based on DAS28-ESR scores (p=0.24). Rituximab showed greater improvement in HAQ scores over time than the TNFis (p=0.0391). Both groups reported similar types and numbers of serious adverse effects. Rituximab was found to be more cost-effective than TNFis (p<0.0001).

Literature Review

T-cell inhibitors

- Hetland et al. (2020) performed a randomized, assessor-blinded phase 4 trial to assess the benefit and safety of treatment of patients with early RA with either the TNFi (certolizumab pegol), a T-cell inhibitor (abatacept), or the interleukin-6 inhibitor (tocilizumab), plus MTX compared to conventional treatment with DMARDs. They found that abatacept was superior to conventional therapy (52% CDAI remission). Similar numbers and types of adverse effects were noted in all treatment groups.
- Westhovens et al. (2009) conducted a multi-national, randomized, double-blinded, two-year clinical trial to evaluate the efficaciousness and safety of abatacept in the treatment of RA compared to MTX. The treatment group showed higher rates of remission using DAS28-CRP scores, improved ACR50/70 responses, improved HAQ-DI scores, and lower radiographic progression of disease after one year (p<0.01 in all measures). The researchers also described a more favorable safety profile of abatacept than the placebo group.



Discussion

- Scott et al. (2014) evaluated treatment with TNFis vs cDMARDS and found similar DAS28 scores between the two, but the EQ-5D scores suggested worse disease progression in the cDMARD treatment.
- The study by Corrado et al. (2017) evaluated which TNFi produces the greatest result, which showed that the particular TNFi used was not significant; all three of the widely used choices produced similar results.
- Hetland et al. (2020) compared the use of T-cell inhibitors, ILis, and TNFis, and found that all three treatments had similar outcomes. Genovese et al.. (2018) also directly compared treatment with ILis and TNFis and found they both had similar outcomes as well.
- Porter et al. (2016) also directly compared potential therapies, evaluating the use of TNFis to B-cell inhibitors and found similar results between the groups, except that HAQ scores over time were better when treating with the B-cell inhibitor.
- Behrens et al. (2021) also analyzed the use of B-cell inhibitors, this time comparing the use of the B-cell inhibitor plus LEF to that of LEF alone. Their results showed benefit in DAS28 scores and remission of CDAI scores after 24 weeks using the B-cell inhibitor plus LEF, offering this type of combination therapy as another option for treatment. Westhovens et al. (2009) evaluated another type of combination therapy, comparing the use of T-cell inhibitors plus MTX to treatment with a placebo and MTX and found that the combination therapy resulted in reduced DAS28 scores and better ACR responses. Other analyses of combination therapy by Hetland et al. (2020), Feist et al. (2022), and Genovese et al. (2018) highlighted that combination treatment with IL-6 or IL-17 plus MTX shows benefit as well, suggesting combination therapy should be considered.
- This research suggests that any choice of biologic, whether ILi, TNFi, B-cell inhibitor, or T-cell inhibitor may be good options to offer patients with RA. However, more analysis is required to eliminate the questions of generalizability and potential biases within the research.
- It is important not to discount the importance of vitamin D and its potential benefits in treatment. The research by Buondonno et al. (2017) showed that those with RA have significantly decreased vitamin D levels than those without the disease. They also found improvement in GH related to incorporating vitamin D into standard treatment of RA.
- The research by Li et al. (2018) showed decreased ESR and CRP, improved HAQ-DI, decreased VAS scores, and decreased morning stiffness with vitamin D alone.
- While biologics are promising options for therapy to slow or stop progression of disease, vitamin D has encouraging potential in the prevention of disease and as a therapy adjunct. With its safe nature, there is likely little risk in its addition to therapy; however, further analysis that provides generalizable results is still required before we can recommend the best, most personalized treatment option for patients.
- The choice of treatment for RA is complex and depends on several factors, including patient-specific goals for treatment, individual patient characteristics, disease severity, risks and side effects, and cost. The safety and effectiveness of treatment can vary among patients and since every patient's case is unique, the possibility of having a universal treatment for RA is very unlikely. After a provider thoroughly evaluates a patient's condition, the selection of a treatment plan should entail collaborative decision-making between a healthcare provider and a patient.

Applicability to Clinical Practice

- This research highlights the complexity of RA management.
- Patients and providers must recognize modifiable risk factors for disease and intervene early.
- Knowing the effects of treatment vary widely among patients makes it imperative to create individualized treatment plans that account for patient factors such as disease severity and goals of treatment. Additionally, it is important to consider the chronic nature of RA when selecting treatments, choosing options that not only offer short term benefit, but provide long term effects and that are sustainable over several years.
- Providers should be prepared to continually reassess and modify treatment as needed. With this, patients and providers should be open to a trial-and-error approach to treatment, knowing there is no universal regimen, and consider combination therapy with DMARDS, biologics, and other adjunctive therapy such as vitamin D, to combat the different aspects of the disease.
- It is important for providers to stay informed about current research and treatment strategies as new evidence emerges, such as with the addition of vitamin D to treatment regimens and release of new biologics with better side effect profiles, in order to best meet the needs of individual patients.

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