REVIEWS

Immunomodulators in managing geriatric rheumatoid arthritis

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Abstract

Immunosenescence, the aging of immune system, is known to be a risk factor for infection and cancer. Advanced age has been associated with a wide range of disorders linked to both innate and adaptive immune systems. Further, the associated comorbidities like diabetes, renal failure, malignancy etc., lead to an immunosuppressed state, which needs greater precautions. Age also modifies drug-related pharmacokinetic parameters like absorption, distribution, metabolism, and excretion. All these factors warrant cautious use of immunomodulators in elderly rheumatoid arthritis (RA) patients. Moreover, majority of the clinical trials exclude the elderly population and limit their studies only to younger subjects. This selection bias, along with limited studies on geriatric population, makes the management of this special group of patients very challenging. Even though, the present evidence from clinical trials suggests that DMARDs and biologic agents have good efficacy and safety profile in elderly patients with RA, such individuals are often undertreated. The present data is not sufficient for the development of evidence-based guidelines for this population. Thus, additional clinical studies focusing on pharmacokinetics, efficacy, and safety of immunomodulators in elderly patients are warranted.

Introduction

The proportion of elderly rheumatoid arthritis (RA) patients worldwide is on the rise and approximately 30% of RA cases occur in this age category. Co-occurrence of other disease in geriatric patients often influences the management of rheumatic diseases. Drug toxicities greatly impact the patient outcome in RA and can present unique challenges in older individuals. The quality of life in elderly patients can be greatly improved by the judicious use of immunomodulatory drugs and through increased awareness, monitoring, and prevention of medication side effects. This review focuses on the latest data pertaining to the use of traditional DMARDS and the newer biologic therapies in the geriatric rheumatoid patients.

Concerns related to the use of immunomodulators

Recent years have witnessed a steady increase in the overall frequency of DMARD use, but older individuals are less likely to receive DMARDs compared to younger patients.[1] In large cohorts like, the United States veterans with elderly onset RA (EORA) and the North American CORRONA (Consortium of Rheumatology Researchers of North America), it has been shown that the overall usage of DMARDs has increased over the last decade.[1, 2] Elderly patients more often received methotrexate as a single agent and at much lower doses. The use of glucocorticoids was more in this population, with less usage of combination DMARDs and biologic therapy, despite comparable disease severity and activity. These inequalities have been noted in the Dutch and Swedish registries as well, even though elderly patients often have more active disease.[3] These findings were further confirmed in the Swiss registry, which showed that glucocorticoids were used as first-line treatment in 68% of elderly vs. 25.4% of younger patients, and the biological DMARDs were less commonly used during follow-up.[4]

Apprehensions on drug-related side effects, both in physicians and patients, limit the extensive use of DMARDs. The use of immunomodulators in elderly is even more complicated due to their increased susceptibility to contract infections than the young counterparts. However, many recent studies are reassuring in this aspect, as the findings indicate that the toxicities associated with DMARD use in elderly are low or comparable to younger RA patients. Therefore, the elderly with RA should not be denied from receiving optimal treatment with these medications.

Need for better management strategies

It has been proven that better control of RA has direct impact on morbidity and mortality. The present aggressive treatment strategies of 'tight control' and 'treat to target' have revolutionized the management of RA. With the addition of newer biologic DMARDs and judicious use of traditional DMARDs, we have been able to effectively customize these strategies in majority of the patients. However, the use of these management strategies is often restricted in elderly RA patients, mainly because of the lack of proven evidence on efficacy and safety. The need of the hour is to extend the benefits of these newer strategies to improve disease severity and functional capacity of elderly patients in order to improve the quality of life.

Management considerations

The goals of management in both elderly and younger RA populations are the same i.e to decrease inflammation and prevent destruction of the joints in a safe and effective manner. The presence of comorbid diseases, frailty, and fear of toxicity are deterring rheumatologists from using aggressive strategies to treat elderly patients.[1] The following sections deal with the pharmacokinetics, efficacy, and safety profiles of the most commonly used DMARDs in the elderly, including methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ), and hydroxychloroquine (HCQ), and also the role of biologic DMARDs.

a. Methotrexate

Pharmacokinetic studies of MTX have shown that its clearance is highly correlated with creatinine clearance and inversely with the age.[5] The dosing regimen should be adjusted in elderly patients according to the renal function rather than the age. Regarding efficacy, meta-analysis of available trials has demonstrated that MTX is one of the most effective medications and is recommended as the first line of choice for the treatment of RA.[6, 7] Pooled data from 11 clinical trials with 496 RA patients have shown that the age did not affect MTX efficacy on tender/swollen joint count, erythrocyte sedimentation rate, and pain.[8] These studies suggest that the efficacy of MTX is comparable in elderly and younger RA populations.

Around 10 to 30% of patients receiving MTX discontinue this drug secondary to adverse effects, but most of these adverse events are mild and may not lead to treatment termination. Meta-analysis of the available clinical trials has shown that even subjects belonging to the oldest age group (≥ 70 years) were not at higher risk of side effects from MTX. However, patients with renal impairment had a higher overall rate of toxicity and were at higher risk of severe respiratory toxicities than those with normal creatinine clearance.[8] In a large North America registry (CORRONA) of 1953 RA patients treated with MTX, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased above the upper normal limit in 22% subjects, and 1% had a two-fold increase in these enzymes.[9] Independent predictors of abnormal AST values were lack of folate supplementation and untreated hyperlipidemia.[10] Even though elevations in serum transaminases occur frequently, especially in the first 6 months of MTX therapy, serious liver disease is extremely uncommon. In a review, published in 1977, hepatotoxicity was found to be more common in the elderly patients, although evidence was sparse.[11] Late age at first use of MTX and duration of the therapy were found to be independent predictors of serious liver disease. In a much recent study, involving a large cohort of patients with RA and psoriatic arthritis receiving MTX, LEF, and both in combination or other non-biologicals or TNF inhibitor DMARDs, it was observed that age was not an independent predictor of hepatotoxicity.[10] The current evidence shows that MTX has a very good safety profile in elderly, comparable to younger patients.

b. Leflunomide

Leflunomide is a prodrug, which is rapidly converted in the submucosal wall of the intestine, plasma, and liver into active metabolite. The mechanism of action is different from that of MTX and many studies have shown that its efficacy is comparable to that of MTX.[12-14] Specific pharmacodynamic or pharmacokinetic studies of the drug have not been done in the elderly.

Clinical trials involving a total of 1339 patients, treated with LEF monotherapy, have shown that the frequency of adverse effects and the safety profile of LEF were comparatively similar to those on moderate-dose MTX and SSZ. None of the studies have evaluated the safety profile of LEF exclusively in elderly population. However, Chan *et al.* in 2004 has reported 19 cases of pancytopenia associated with LEF use in Australia.[15] The authors concluded that the risk for pancytopenia increased with concomitant use of MTX and in older patients. Hypertension, which can occur as a side effect of LEF, is another major concern in elderly population. Data from clinical trials suggests that aggravation of existing hypertension is more likely to be a problem with LEF than new-onset hypertension.[16]

c. Sulfasalazine

The pharmacokinetic studies of SSZ in elderly RA patients have shown that the acetylator phenotype, but not age, plays a role in determining the serum concentration of sulfapyridine.[17] SSZ is likely to be as effective as lower doses of MTX, although it is usually no longer recommended as monotherapy for RA.[18] In a randomized controlled study, published in 1983, elderly patients were found to have a higher dropout rate due to the occurrence of nausea and vomiting than younger patients.[19] However, a combined analysis of five prospective SSZ studies, in which they have looked specifically for side effects in different age groups showed that no age-related differences in either toxicity or efficacy were seen.[20]

d. Hydroxychloroquine

There are no studies specifically examining the pharmacodynamics or pharmacokinetics of HCQ in the elderly population. When compared to other immunosuppressive and biologic therapies, the relative effectiveness of HCQ is smaller; however, the drug is often used as adjunctive therapy in combination regimens for RA. A meta-analysis evaluating the efficacy of antimalarials for RA indicated that they have moderate efficacy when used alone for the treatment of RA.[21]

Antimalarials are considered to be very safe in RA patients. Although rare, the major adverse reaction of the treatment is maculopathic retinopathy and it is considered as a contraindication for using these drugs. The 2011 guidelines on screening for chloroquine and HCQ retinopathy recommend conducting baseline examinations in patients receiving antimalarials to serve as a reference point and to rule out maculopathy.[22] Annual screening should begin after 5 years or sooner if there are unusual risk factors. Elderly patients are considered to be at higher risk, given the possibility that age-related changes within the retina could increase the susceptibility to toxic damage. The assessment of toxicity is also more difficult in the elderly because of the difficulty in recognizing bull's-eye depigmentation due to the diffuse loss of fundus pigmentation with age. If the baseline examination does not reveal any contraindication, HCQ can be used in this high-risk group, with more frequent screening done at least once in a year.

e. Biologics

Biologics have expanded and improved the therapeutic armamentarium for RA and have resulted in tight control and dramatic improvement in patient outcomes. Despite the proven efficacy and safety profile, a growing proportion of the elderly RA patients does not receive biologic agents. Deterring the use of these drugs due to safety concerns, results in exposure to more deleterious drugs such as glucocorticoids and NSAIDs in most cases. This review focuses on anti-TNF agents and rituximab, since the evidence regarding other biologic agents in elderly is sparse.

The pharmacology of therapeutic monoclonal antibodies is complex and depends on the structure of the antibody, the properties of the target antigen, patient characteristics, and disease-related factors. To date, only limited information is available regarding the factors, other than the formation of neutralizing antibodies that influence the pharmacokinetics of monoclonal antibodies.[23]

Younger patients were found to have better clinical outcomes in a large German study and in the ReAct study.[24, 25] However, no association with gender or age and clinical response was found in the British Society for Rheumatology Biologics Register (BSRBR) and the retrospective South Swedish Arthritis Treatment Group Register. [26, 27] The most recent review, focusing on the use of anti-TNF in RA, has confirmed that the benefit/risk balance barely declines with age.[28]

In the CORRONA registry, toxicities related to treatment with biological DMARDs or other DMARDs were found to be similar in patients above and below 60 years of age.[1] Many studies, done specifically in the elderly population, did not find an increased risk of serious infection associated with initiation of anti-TNF therapy for RA compared to non-biological comparators.[29-31] One recent study from South Korea, which has specifically evaluated the risks of reactivation of tuberculosis, has shown that elderly patient aged >60 years had a significant risk for this complication. Due to the lack of data in elderly subjects and on long-term follow-up, it is uncertain whether the use of biologics is linked to increased risk of cancer. In a recent review on biologics treatment in elderly, the authors concluded that the specific risk profile of TNF antagonists in the elderly suggests a trend towards an increased risk of serious infection, tuberculosis reactivation and skin cancer compared with non-biologic comparators.[28]

In a recent study from the French society of Rheumatology, 1709 RA patients were specifically analyzed for any age-

Table 1: Precautions to be considered while using immunomodulators in elderly

Immunomodulators	Special precautions
Methotrexate	a. Dose adjustment as per creatinine clearance[5] a. Monitor for hepatotoxicity[11]
Leflunomide	a. Monitor blood pressure[16] b. Watch for cytopenia[15]
Sulfasalazine	a. Mild increase in occurrence of gastrointestinal side effects [19]
Hydroxychloroquine	a. High risk for maculopathy[22] b. Annual screening should begin from the start of therapy[22]
Anti-TNF	a. Trend towards increased risk of tuberculosis reactivation and skin cancer[28]
Rituximab	a. Less effective in very elderly (>75 years) b. Increased risk of severe infections[32]

related effect on efficacy and safety of rituximab.[32] The researchers have concluded that rituximab is effective in the elderly, and to a lesser extent in the very elderly (age >75 years). Infections were more severe in the elderly and very elderly than in younger subjects. Thus rituximab may be prescribed in elderly if they do not respond to anti-tumor necrosis factor treatment or if the latter is contraindicated and carefully monitoring for any serious infections.

Conclusion

DMARDs, both conventional and biologic, have promoted the development of tight control and led to a dramatic improvement in patient outcomes. Unfortunately, these benefits have not been utilized effectively in the elderly RA patients. In these patients, the target and choice of therapy should be tailored according to disease activity and severity, comorbidities, and the risk factors for adverse effects of drugs. The present evidence suggests that DMARDs are effective and are well tolerated in the elderly RA patients. However, additional clinical studies are warranted in this group, with treatment regimens tailored according to aging process.

Key points

- The number of elderly patients with RA is increasing worldwide.
- Present data suggests that the elderly RA patients are undertreated and need better control of the disease. DMARDs have been shown to be equally effective and well tolerated.
- The choice of DMARDs should be tailored according to the comorbidities and the risk of adverse reactions. Methotrexate is the first choice, even in elderly RA patients, and the dose should be calculated according to creatinine clearance.
- Additional clinical data is required to develop evidence-based guidelines specific for this population.

Competing interests

The authors declare that they have no competing interests.

Citation

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