Treatment of the elderly rheumatoid arthritis patient

Edward Melikterminas, Veena Ranganath & Daniel E Furst†

†Author for correspondence University of California, Los Angeles, Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, 1000 Veteran Avenue, Room 32–59, CA 90025-167O, USA Tel.: +1 310 794 9504; Fax: +1 310 206 8476; defurst@mednet.ucla.edu

Rheumatoid arthritis (RA) is a destructive inflammatory arthritis of unknown origin. With the advent of DMARDs and biological agents, the goal of treatment is the induction of remission and prevention of tissue damage in both the elderly and the general RA population. Aging, in particular, can be associated with a decline in the physiologic function of body organs, as well as considerable changes in pharmacodynamics and pharmacokinetics. This makes treatment challenging in elderly RA patients. Thus, a treatment plan must be tailored to meet the severity of the disease and to account for the presence of any comorbidities, especially in the elderly, who may be more frail. Adverse events, such as an increased incidence of infections and malignancy, in some elderly RA patients might be attributed to increased comorbidities with physiologic aging rather than the patient's chronological age. In particular, this applies to the natural decrement in immunoregulation that occurs in the elderly. In summary, the treatment of RA in the elderly is not different from the treatment of RA in the young once one considers the comorbidities associated with the normal decrements and changes in pharmacokinetics (e.g., change in renal and hepatic function) and pharmacodynamics (e.g., immunosenescence) that are associated with aging.

Rheumatoid arthritis (RA) is a destructive inflammatory arthritic disease that has an incidence of approximately 1% in the general population, with approximately a third of these patients having onset of RA above the age of 65 years [1]. The incidence of RA increases dramatically with age, with a fivefold increase in incidence from the age of 35 to 75 years (20 vs 100 per 100,000), and the prevalence of elderly RA is approximately 2% [2]. We will briefly review the physiologic, pharmacokinetic and pharmacodynamic changes that occur and apply that to the RA population. We will then briefly review the data regarding the use of DMARDs in the elderly RA patient. Finally, we will suggest an approach to the future use of these drugs in the elderly RA patient, and propose potential research to improve their care

Physiologic & pharmacodynamic changes with aging

Aging results in decreasing function of organ systems [3]. At the same time, there are changes in pharmacokinetics and pharmacodynamics that occur with aging.

Absorption is not affected by age, although the transit time through the GI tract increases [4]. However, aging does affect distribution of medications and depends on cardiac output, protein binding, total body fat and water composition. Cardiac output is decreased, leading to decreased perfusion of the tissues, while the increased percentage fat in the elderly leads to altered drug distribution [5–8]. Decreases in the volume of distribution of hydrophilic compounds, such as methotrexate, and decreased clearance of lipophilic compounds, such as diazepam, leflunomide and piroxicam, could potentially occur [9]. However, little work has been done to evaluate changes in the volume of distribution of antirheumatic drugs with age.

The smooth endoplasmic reticulum of the liver cell is the principal site of drug metabolism, and aging reduces liver mass and blood flow [9]. Aging principally affects phase I reaction CYP enzymes (oxidation, reduction and hydroxylation) [10]. Type II reactions (e.g., glucuronidation), the main pathway to metabolize many drugs in humans, are not significantly affected [11].

Clearance is additive across metabolic and excretory pathways, and total clearance includes renal, metabolic and biliary components. In addition, some drugs are excreted in saliva, sweat and breast milk and are even exhaled [12].

However, most drugs are eliminated largely by the kidneys, particularly water-soluble drugs and their metabolites. The glomerular filtration rate decreases by approximately 1 ml/min/year between the ages of 40 and 80 years [13]. Thus, clearance of many drugs, such as water-soluble antibiotics [14], diuretics [15] and NSAIDs [16,17], decreases with aging and

Keywords: antirheumatic drug, DMARD, elderly, rheumatoid arthritis

dose modification may be necessary. More interestingly, it has been observed that a reduction in renal function may not only affect the elimination of renally excreted drugs, but also of drugs undergoing extensive metabolism in the liver [18,19].

There is also differential sensitivity to medications in the elderly. An example of this is increased sensitivity to warfarin and decreased responses to salbutamol and propranolol in elderly patients. The precise mechanisms of these effects are not understood, although it has been speculated that the number or affinity of receptors has been changed [20].

Finally, immunosenescence, a deterioration of the cellular and/or humoral immune system with aging, has been proposed as a mechanism leading to the development of increased risk of infection, cancer and autoimmune diseases. Thymic atrophy, leading to decreased numbers of naive T cells with aging, may contribute to an increased susceptibility to certain autoimmune disorders [2]. The breakdown of control of the elderly humoral immune system leads to an increased prevalence of autoantibodies, including rheumatoid factor and antinuclear, antiphospholipid, anti-smooth muscle and antimitochondrial antibodies [21].

DMARDs in the elderly

Methotrexate is the first-line agent for rheumatoid arthritis (RA) in the USA and Europe. A retrospective study compared 2101 older-onset RA patients (aged 60–70 years) with a matched set of younger RA patients. Methotrexate was more commonly used by older-onset RA patients; however, the weekly methotrexate dose was lower (median: 11.25 mg) than those with younger-onset RA (median: 16.25 mg) [22], and the older-onset RA patients had less methotrexate-related toxicity. In a study evaluating intramuscular methotrexate pharmacokinetics in 38 older RA patients (aged 65–83 years) and 24 younger RA patients (aged 21–45 years) [23], the elimination half-life of free and total methotrexate was greater in the elderly RA group, which may be related to decreased methotrexate renal clearance in the elderly patients [24].

Sulfasalazine is as effective in the elderly as it is in the young. The literature suggests that the slow-acetylator phenotype rather than age plays a role in determining elevated 'steady-state' serum concentrations, ultimately potentially leading to toxicity [25].

Chloroquine and hydroxychloroquine are cleared by both renal and hepatic pathways. The elderly have decreased renal function and selectively decreased hepatic metabolism. Patients with higher risk of toxicity include: patients aged over 60 years; those with known retinal disease, visual impairment, or renal or liver impairment; those receiving a daily dose greater than 6.5 mg/kg; or those who have received an accumulated dose above 500 g [26]. In addition, the increased frequency of cataract and macular degeneration in the elderly might make it difficult for appropriate chloroquine and hydroxychloroquine toxicity screening [27].

There are few available data regarding leflunomide use in the elderly; however, some European rheumatologists advise caution in leflunomide-treated patients with comorbidities [28].

Biologic agents

Etanercept is a TNF inhibitor that binds to TNF-α, preventing it from interacting with its receptor. Data regarding etanercept from 18 RA, two psoriatic arthritis and two ankylosing spondylitis trials with 4322 patients revealed no significant differences in serious adverse events, infections, deaths and malignancies in elderly compared with younger subjects [29,30].

Infliximab is a chimeric TNF-blocking antibody. In two infliximab studies involving 181 RA patients aged 65 years or older compared with younger patients, no overall differences were observed in efficacy or safety. According to another observational study evaluating 83 patients with RA, there was a 6.5-fold higher incidence of withdrawal from the study owing to severe infections in older patients, with 13% (only 11 patients) being older than 70 years. Further studies involving elderly patients are needed [31].

Adalimumab is a human anti-TNF monoclonal antibody. In an adalimumab trial evaluating 519 patients aged 65 years and older, there was no significant difference in efficacy compared with a younger RA group. However, there was an increased incidence of serious infections and malignancy in older RA patients [32]. The authors feel that this may be attributed to a higher incidence of infections and malignancy in the general elderly population; however, this specific question was not analyzed.

Anakinra is an IL-1 receptor antagonist. In a 6-month, double-blind, placebo-controlled study conducted in 169 centers, the incidence of adverse events in patients with different

comorbidities (including those with heart failure, kidney disease and diabetes mellitus) was similar in the placebo and anakinra groups, although the study was conducted among patients with a large range of ages (95% CI: 34.2–81.4 years) [33]. The implication, not specifically analyzed, is that there was no greater toxicity among the elderly and young RA patients. In a clinical trial involving 635 patients aged over 65 years, no overall differences in safety or efficacy were observed between elderly and younger patients [34].

There are insufficient published data regarding other biological agents, such as rituximab or abatacept, to comment on the use of these drugs in the elderly.

Conclusion & future perspective

It is clear that human physiology undergoes multiple changes with aging. This is true in terms of the way that medications are handled by the body, changes in general organ function and, specifically, immunologic surveillance and response. Our brief review of human physiology and published data regarding the use of DMARDs in the elderly is intended to point out some of these factors.

From the data presented above, one can draw the conclusion that there may be several 'populations' of elderly patients with rheumatic diseases. There are the 'frail elderly', whose cardiac and renal function are decreased, who have multiple comorbidities, including hypertension, diabetes, and decreased renal and cardiac function, and who may demonstrate some impairment in thinking, memory and so on. The frail elderly may also have relatively decreased homeostatic mechanisms to control their immune function, allowing the appearance of autoimmune phenomena.

These patients can be contrasted with the 'robust elderly', who are physiologically young for their age. They are mentally active, their hearts and kidneys continue to function with high efficiency, their liver function remains robust and their immune system maintains excellent homeostasis.

It is probable that the robust elderly make up a large proportion of patients entering clinical trials. It is no wonder, then, that many studies (such as some of those quoted above) seem to indicate little difference in response and no great increase in toxicity. Data from these trials would make one, appropriately, want to treat certain elderly patients more aggressively than is presently being done, fearing that this group of patients is being undertreated [34,35]. For this group of robust elderly, such an approach – treating more aggressively – may be reasonable and very appropriate.

However, a problem could arise if one were to extrapolate these clinical results to the whole of the elderly population. Those frail elderly who do not enter studies may well have a very different response to therapy and a higher propensity to side effects from medications. The real issue, then, is to be able to separate the robust elderly from the frail elderly. In oncology, the Charlson's comorbidity index was developed to predict the risk of mortality/morbidity. This index predicts the 1-year mortality for patients, using 22 comorbid conditions such as heart disease, AIDS or cancer [36]. We believe that developing such an index for the rheumatic diseases would represent a way forward towards individualizing therapy – and it could be applied to younger patients as well as the elderly. One would, in essence, consider the physiological rather than the chronological age of patients.

Lacking a predictive algorithm, rheumatologists will have to use more qualitative mechanisms, such as the presence of multiple comorbidities *per se* and knowledge of a given patient's general organ function (e.g., low albumins, elevated creatinine), and treat this subgroup of patients with gentle caution. Meanwhile, the 'other' group of patients, the qualitatively robust elderly, may be treated more 'assertively' to push towards excellent clinical response with higher doses of medications, so long as appropriate and usual caution is taken.

Financial & competing interests disclosure

Daniel E Furst has received honoraria, consultation fees or research grants from Abbott, Amgen, Centocor, Genentech, Roche and BMS. He has no disclosures regarding employment, stock ownership or options, expert testimony, royalties or grants pending. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Drosos AA: Methotrexate intolerance in elderly patients with rheumatoid arthritis: what are the alternatives? *Drugs & Aging* 20(10), 723–736 (2003).
2. St Clair EW, Pisetsky DS, Haynes BF: *Rheumatoid Arthritis (1st Edition)*. Lippincott Williams & Wilkins, PA, USA (2004).
3. Mangoni AA, Jackson SH: Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br. J. Clin. Pharmacol.* 57(1), 6–14 (2004).
4. Mayersohn M: Pharmacokinetics in the elderly. *Environ. Health Perspect.* 102(Suppl. 11), 119–124 (1994).
5. Ogawa T, Spina RJ, Martin WH 3rd *et al.*: Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 86(2), 494–503 (1992) .
6. Beyth RJ, Shorr RI: Principles of drug therapy in older patients: rational drug prescribing. *Clin. Geriatr. Med.* 18(3), 577–592 (2002).
7. Turnheim K: When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp. Gerontol.* 38(8), 843–853 (2003).
8. Ranganath VK, Furst DE: Disease modifying drug use in the elderly RA patient. *Rheum. Dis. Clin. North Am.* 33, 197–217 (2007).
9. Mangoni AA, Jackson SH: Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br. J. Clin. Pharmacol.* 57(1), 6–14 (2003).
10. Rawlins MD, James OFW, Williams FM, Wynne H, Woodhouse KW: Age and the metabolism of drugs. *Q. J. Med.* 64(243), 545–547 (1987).
11. Schmucker DL, Vesell ES: Are the elderly underrepresented in clinical drug trials? *J. Clin. Pharmacol.* 39, 1103–1108 (1999).
12. Kreuer S, Bruhn J, Wilhelm W, Bouillon T: Pharmacokinetic–pharmacodynamic models for inhaled anaesthetics. *Anaesthesist* 56(6), 538–556 (2007).
13. Lindeman RD, Preuss HG: Renal physiology and pathophysiology of aging. *Geriatr. Nephrol. Urol.* 4(2), 113–120 (1994).
14. Lumholtz B, Kampmann JJ, Siersbaeck-Nielsen K, Hansen JM: Dose regimen of kanamycin and gentamycin. *Acta Med. Scand.* 196, 521–524 (1974).
15. Somogyi A, Hewson D, Muirhead M, Bochner F: Amiloride disposition in geriatric patients: importance of renal function. *Br. J. Clin. Pharmacol.* 29, 1–8 (1990).
16. Oberbauer R, Krivanek P, Turnheim K: Pharmacokinetics of indomethacin in the elderly. *Clin. Pharmacokinet.* 24, 428–434 (1993).
17. Morgan J, Furst DE: Implications of drug therapy in the elderly. *Clin. Rheum. Dis.* 12, 227–244 (1986).
18. Yuan R, Venitz J: Effect of chronic renal failure on the disposition of highly hepatically metabolized drugs. *Int. J. Clin. Pharmacol. Ther.* 38, 245–253 (2000).
19. Rostami-Hodjegan A, Kroemer HK, Tucker GT: *In vivo* indices of enzyme activity the effect of renal impairment on the assessment of CYP2D6 activity. *Pharmacogenetics* 9, 277–286 (1999).
20. Jackson SHD: Pharmacodynamics in the elderly. *J. R. Soc. Med.* 87(Suppl. 23), 5–7 (1994).
21. Juby AG, Davis P, McElhaney JE, Gravenstein S: Prevalence of selected autoantibodies in different elderly subpopulations. *Br. J. Rheumatol.* 33(12), 1121–1124 (1994).
22. Tutuncu Z, Reed G, Kremer J, Kavanaugh A: Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? *Ann. Rheum. Dis.* 65, 1226–1229 (2006).
23. Bressolle F, Bologna C, Kinowski JM *et al.*: Total and free methotrexate pharmacokinetics in elderly patients with rheumatoid arthritis. A comparison with young patients. *J. Rheumatol.* 24(10), 1903–1909 (1997).
24. Olivieri I, Palazzi C, Peruz G, Padula A: Management issues with elderly-onset rheumatoid arthritis. *Drugs Aging* 22(10), 809–822 (2005).
25. Wilkieson CA, Madhok R, Hunter JA, Capell HA: Toleration, side-effects and efficacy of sulphasalazine in rheumatoid arthritis patients of different ages. *Q. J. Med.* 86, 501–505 (1993).
26. May K, Metcalf T, Gough A: Screening for hydroxychloroquine retinopathy. *BMJ* 317(7169), 1388 (1998).
27. Kline DW, Li W: Cataracts and the aging driver. *Ageing Int.* 30(2), 105–122 (2005).
28. Maddison P, Kiely P, Kirkham B *et al.*: Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxf.)* 44(3), 280–286 (2005).
29. Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P: Long term safety of etanercept in elderly subjects with rheumatic diseases. *Ann. Rheum. Dis.* 65, 379–384 (2006).
30. Bathon JM, Fleischmann RM, van der Heijde D *et al.*: Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J. Rheumatol.* 33(2), 234–243 (2006).
31. Chevillotte H, Ornetti P, Mistrih R *et al.*: Survival and safety of treatment with infliximab in elderly population. *Rheumatology (Oxf.)* 44(5), 695–696 (2005).
32. Keystone E, Haraoui B: Adalimumab therapy in rheumatoid arthritis. *Rheum. Dis. Clin. North Am.* 30(2), 349–364 (2004).
33. Schiff MH, DiVittorio G, Tesser J *et al.*: The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. *Arthritis Rheum.* 50(6), 1752–1760 (2004).
34. Kineret® (anakinra), summary of product characteristics. Amgen Europe BV, Breda, The Netherlands (2003).
35. Schmajuk G, Schneeweiss S, Katz JN *et al.*: Treatment of older adult patients diagnosed with rheumatoid arthritis: improved but not optimal. *Arthritis Rheum.* 57(6), 928–934 (2007).
36. Fraenkel L, Rabidou N, Dhar R: Are rheumatologists' treatment decisions influenced by patients' age? *Rheumatology (Oxf.)* 45(12), 1555–1557 (2006).

Affiliations

- *Edward Melikterminas, MD*
  University of California, Los Angeles, Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, 1000 Veteran Avenue, Room 32–59, CA 90025-167O, USA
- *Veena K Ranganath, MD*
  University of California, Los Angeles, Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, 1000 Veteran Avenue, Room 32–59, CA 90025-167O, USA
- *Daniel E Furst, MD*
  University of California, Los Angeles, Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, 1000 Veteran Avenue, Room 32–59, CA 90025-167O, USA
  Tel.: +1 310 794 9504
  Fax: +1 310 206 8476
  defurst@mednet.ucla.edu