Treatment of elderly rheumatoid arthritis

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This review summarizes the current approach to treating rheumatoid arthritis in the elderly and outlines the side effects encountered with the use of antirheumatic agents, including antitumor necrosis factor agents, in this population. With the aging of the western population, the prevalence and incidence of rheumatoid arthritis is increasing among elderly persons. The management of rheumatoid arthritis in the elderly requires special consideration with regards to comorbidities and the potential for an increased frequency of adverse events. There is a substantial need for optimizing various aspects of the diagnosis and therapy of arthritis in an effort to reduce the impact of inflammatory arthritis in the growing elderly population.

Rheumatoid arthritis (RA) is the most common inflammatory arthritis in older adults. It is now known to increase in incidence and prevalence up to 85 years of age. The prevalence of RA in persons of 60 years of age and older is reported to be approximately 2% [1]. There is potential heterogeneity among elderly persons with RA. For example, since there is presently no cure for RA, an older person with RA may have been diagnosed with the disease at a much younger age, and yet may still be suffering the effects of the disease into their later years. Alternatively, an older person may develop RA *de novo* later in life. In the literature, there is controversy about whether those with younger-onset RA (YORA) differ from those with elderly-onset RA (EORA) with regards to characteristics such as signs and symptoms or outcomes of disease. Importantly, if one compares older persons with YORA, with those with EORA, the most important confounder is probably disease duration. Those older persons with YORA commonly have an advanced stage of the disease, having had the condition for many years. They have often received therapy with multiple agents and may be refractory to treatment. Not uncommonly, they have undergone elective joint surgery. The physical examination of these patients may reveal varying degrees of polyarticular synovitis and deformities in both the upper and lower extremities. Systemic manifestations, such as rheumatoid lung, vasculitic ulcers, peripheral neuropathy and secondary amyloid, all reflect long-standing inflammatory disease and may complicate the care of this population of RA patients. Within the EORA population an acute onset of disease and prominent elevations in the erythrocyte sedimentation rate (ESR) have been reported as being more common than for YORA [2,3]. Clinically, EORA is said to be characterized by disabling morning stiffness and marked pain, predominantly affecting the upper extremities. The physical examination may be notable for pronounced synovitis of the shoulders and the wrists, as well as the metacarpophalangial joints and proximal interphalangial joints, with marked limitation of motion and severe soft-tissue swelling. The reviews on this arthritis type have stressed that involvement of large joints, in particular shoulder joints, is a striking feature of arthritis in the elderly [4,5].

The diagnosis of RA in the elderly may be particularly complicated since the accuracy of rheumatologic laboratory tests may differ in older versus younger patients. For example, increases in autoantibodies, including rheumatoid factor (RF), are not uncommon in older persons, and therefore have less specificity for the diagnosis of RA than among younger persons. While it is not strictly a criterion for diagnosis, the ESR also increases nonspecifically in older persons, particularly women. Since the ESR can be a marker of systemic inflammation, it may lead to an erroneous suspicion of an inflammatory process in a healthy older person. If such an older person had osteoarthritis, a high ESR and/or RF could lead to an erroneous diagnosis of RA. Indeed, there are a number of different clinical conditions with similar signs and symptoms to RA, such as polymyalgia rheumatica, calcium pyrophosphate deposition disease, gouty arthritis and osteoarthritis, which are more prevalent among the elderly. This can make the diagnosis of RA more difficult in an older population.

The management of RA in elderly patients is complicated not only by diagnostic uncertainty, but also by the increasing presence of comorbid conditions that can affect treatment and changes in

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pharmacokinetics that occur with normal aging. All of these may lead to an increased frequency of adverse drug events [6,7]. While the primary objectives of therapy for RA – to control pain, to stop disease progression and to improve functional status – are similar regardless of age, the efficacy and toxicity of drugs commonly used in RA may differ among the young and aged population.

New agents for the treatment of RA are being investigated in clinical trials. In general, treatment is becoming more aggressive for RA and early intervention is becoming more common. Current strategies include early aggressive treatment with one or more disease-modifying antirheumatic drugs (DMARDs), along with symptomatic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose prednisone.

Nonsteroidal anti-inflammatory agents

In elderly patients, a major consideration with the use of NSAIDs is the increased risk of toxicities, including gastrointestinal (GI) bleeding, renal dysfunction and others. Established risk factors for upper GI bleeding in patients treated with NSAIDs include being aged over 65 years, a history of peptic ulcer disease or other GI bleeding, concomitant use of oral glucocorticoids or anticoagulants and the presence of certain comorbid conditions, such as significant heart disease and emphysema. The risk of upper GI bleeding can be minimized by the use of cyclo-oxygenase (COX)-2 specific NSAIDs or with the concomitant use of proton-pump inhibitors. Risk factors for renal dysfunction include being aged over 65 years, a history of hypertension or congestive heart failure, and concomitant use of diuretics and angiotensin-converting-enzyme inhibitors. Side effects including upper GI toxicity, renal insufficiency and CNS dysfunction are more serious in the elderly than in younger patients [8]. Routine monitoring for toxicity from NSAIDs remains controversial and the side effects can be unpredictable.

In 1998, COX-2 specific inhibitors were introduced to the clinic, with efficacy comparable to that of traditional NSAIDs [9]. Careful monitoring of blood pressure is warranted after initiation of these agents [10,11]. COX-2 inhibitors may be the preferred agents in situations where bleeding is a concern, for example in patients who are on anticoagulant therapy or during the perioperative period, as they do not interfere with platelet function. However, recent data suggest that certain COX-2 inhibitors increase the rate of thrombotic and cardiovascular events [12]. All NSAIDs should be initiated in older persons with the lowest recommended dose, especially in low-weight subjects, since higher plasma concentrations may be detected in elderly patients [13].

Steroids

Some patients may require low-dose oral steroids (often defined as ≤5–10 mg prednisone equivalent per day) when there is a period of flare of their RA or when initiating another drug therapy. The use of low-dose prednisone has been advocated as the second-line therapy in elderly patients with RA, based on the rapid mode of action of steroids and the predisposition of older patients to functionally deteriorate faster than younger populations [14,15]. In one study, a moderate-to-excellent improvement with prednisone therapy was reported in 80 of 91 patients with EORA [15]. However, this therapy can be hazardous, especially in elderly patients, since it poses an increased risk for osteoporosis, infection, glucose intolerance, GI erosive disease, and hypertension. There are data to suggest that with the long-term use of low-dose prednisone, the risk of osteoporosis may outweigh the clinical benefit [16]. Therefore, bone-protective agents and close monitoring of bone density are warranted with chronic usage of steroids.

Intra-articular steroid injections may provide significant relief as sole or adjunctive therapy in some conditions. They can be safely administered to patients if only one or a few joints are inflamed or have caused severe disability. The rationale is to relieve pain, control inflammation rapidly and sometimes avoid administering systemic steroids.

Disease-modifying antirheumatic drugs

DMARD therapy can change the course of RA, resulting in sustained improvement in physical function, decreased inflammatory synovitis and potentially slowing or preventing structural joint damage. Most DMARDs take several months to achieve significant response. Methotrexate (MTX) had been the most effective antirheumatic therapy until the biologics were introduced. Better response rates have been reported with higher doses of MTX, but when used alone it seldom leads to complete remission [17]. Hydroxychloroquine (HCQ) and sulfasalazine (SSZ) are generally preferred in slowly-progressing disease. In addition, since they carry a less toxic profile and need less frequent monitoring, they are the preferred agents

in elderly patients with significant underlying medical problems. Leflunomide is a newer DMARD with a comparable efficacy to MTX. Leflunomide can be used in combination with MTX or in patients who cannot tolerate or have incomplete response to MTX [18]. Cyclosporine A and azathioprine are reserved for refractory patients who have failed other agents. Combination DMARD regimens, for example, MTX plus HCQ plus SSZ or MTX plus cyclosporine, have demonstrated significant clinical improvement when compared with single therapy or placebo [18,19]. Close follow-up and repeated evaluations are required for patients on DMARDs (Table 1). Some studies including patients older than 65 years of age have found no significant effect of age on termination of DMARD treatment [20,21]. However, it has been reported that DMARDs have a tendency to be less effective in older compared with younger patients [20,21]. It should be noted that in these studies prolonged disease duration might have been the key reason for early discontinuation of therapy rather than age, since it is well documented that patients fail to remain on any given DMARD long term.

Table 1. Disease-modifying antirheumatic drugs.

Drug	Side effects	Precautions & monitoring
Methotrexate	GI irritation	Addition of oral folate supplement
	Oral Ulcers	Monitor laboratory tests (LFT, CBC and routine chemistries)
	LFT elevation	Contraindicated in alcoholism, pregnancy (US FDA category X)
	BM suppression	Caution in impaired renal function
	Pneumonitis (uncommon)	Avoid using in Hepatitis B and C
	Nodulosis (uncommon)	Well-tolerated in the elderly
Hydroxychloroquine	GI irritation	Retinal toxicity increases with >70 years of age, 800 g of cumulative dose and >6.7 mg/kg daily dose
	Rash	Ophthalmological test every 6–12 months
	Headache	Caution in hepatic disease, porphyria and psoriasis
	Skin discoloration	
	Retinal toxicity (uncommon)	
Sulfasalazine	GI irritation	Caution in impaired renal function
	Rash	Monitor CBC and LFT every 3-6 months
	Itching	Enteric coated tablets are better tolerated
	Dizziness	
	Headache	
	BM suppression	
Leflunomide	GI irritation	Monitor LFT, routine chemistry and CBC
	Rash	Avoid using in hepatic impairment
	BM suppression	Contraindicated in pregnancy
	LFT elevation	Cholestyramine can be used to reduce plasma levels
Cyclosporine A	Hypertension	Contraindicated in renal failure
	Increased creatinine	Avoid in malignancy
	Hirsutism	Monitor BP and creatinine closely
	Nausea	Monitor chemistries and uric acid
	Tremor	
	Gingival hypertrophy	
Azathioprine	Fever, chills	Caution in hepatic and renal impairment
	GI intolerance	Monitor CBC and differential
	BM suppression	Consider checking TMT enzyme deficiency before initiating therapy
	LFT elevation	

BM: Bone marrow; BP: Blood pressure; CBC: Complete blood count; GI: Gastrointestinal; LFT: Liver function test; TMT: Thiopurine methyltransferase.

Biologics

Antitumor necrosis factor agents

With better understanding of the pathogenesis of autoimmune diseases and advancing developments in biopharmaceutical technology, biologic therapeutic agents have been introduced. These agents target specific components of the immune response, which is considered central to the etiology of RA. Currently there are three antitumor necrosis factor (TNF)-α agents available for clinical use: infliximab, a chimeric anti-TNF-α monoclonal antibody (mAb); etanercept, a soluble TNF-receptor construct and adalimumab, a human anti-TNF-α mAb (Table 2). Different studies including patients with chronic refractory RA, patients with active disease with or without concurrent MTX therapy and patients with early RA demonstrated rapid and sustained improvement with all three agents [9,22,23]. Joint damage, as measured by x-ray progression, appeared to be slowed by these drugs [24–26]. In general, therapy with TNF inhibitors has been well tolerated. These agents represent a major advance in the treatment of severe inflammatory arthritis. However, the greater frequency of concomitant medical conditions (e.g., latent tuberculosis, malignancy, chronic or active infections or a history of congestive heart failure) that may be found in older as compared with younger persons may somewhat limit their usage in this population [27]. Of note, although early clinical trials with anti-TNF agents resulted in an increased incidence of reactivation of latent tuberculosis, patients with latent tuberculosis are allowed to be started on anti-TNF agents if antipulmonary tuberculosis treatment is concomitantly administered. A history of malignancy is not a contraindication for anti-TNF agents, but since there is evidence that there is a dose-dependent increased risk of malignancies in patients treated with anti-TNF agents, clinicians are recommended to be very cautious in initiating these agents.

Although elderly patients were included in most of the clinical trials with anti-TNF agents, evaluations were based on the total enrolled population in the trials. Recently, retrospective subgroup analyses of the response and toxicity rates of the elderly RA patients were determined for some of the clinical trials. Etanercept was found to be safe and effective in elderly patients with RA. In one analysis, 197 of 1128 patients enrolled in four double-blind, randomized trials and five open-label trials with etanercept were 65 years of age and older. It was reported that 55% of patients showed improvement in ACR 20 criteria, a result comparable to that among young patients. In addition, treatment was generally as well tolerated in older persons. In fact, this age group demonstrated a lower rate of injection-site reactions, headache and rash compared with younger patients. Death and cancer diagnoses in patients over 65 years treated with etanercept were similar to the estimated prevalences for these events for this age group within the general population [27]. In another subset analysis of one double-blind trial and two open-label extension trials, the safety and efficacy of etanercept in elderly (age >65 years) and younger adults (age <65 years) treated for early or late-stage RA were compared. Rates of serious adverse events tended to be higher in elderly than in younger subjects; however, rates of safety events observed in elderly etanercept-treated subjects did not exceed rates in elderly placebo or MTX-treated subjects. Elderly subjects tended to have somewhat less robust responses to treatment than younger subjects. However, for both age groups, treatment with etanercept resulted in improved efficacy and function compared with control treatment; and combination treatment with etanercept plus MTX resulted in greater efficacy than either etanercept or MTX used alone. The progression of joint damage as assessed by analysis of serial radiographs of hands and feet was lower after 1 year in subjects treated with etanercept plus

Table 2. Comparison of anti-TNF agents.

	Etanercept	Infliximab	Adalimumab
Half-life	3–4.8 days	8–9.5 days	10–13.6 days
Binding target	TNF-α/LT-α	TNF-α	TNF-α
Administration	Twice or once weekly sc.	Every 4–8 weeks iv.	Every other week sc.
Side effects	Risk of increased infection, drug-induced SLE, autoantibody formation, demyelinating disease, injection-site reaction, hematologic cytopenias and congestive heart failure		

iv.: Intravenous; LT: Lymphotoxin; sc.: Subcutaneous; SLE: Systemic lupus erythmatosus; TNF: Tumor necrosis factor.

MTX compared with subjects treated with either agent alone [28]. Patient-reported outcomes from multiple controlled and open-label extension studies with etanercept were analyzed in elderly and younger adult patients. Improvements in health assessment questionnaire-disability index (HAQ-DI) and proportions of patients achieving an improvement and worsening in HAQ-DI were assessed in elderly versus young patients using data from multiple controlled and open-label extension studies. Elderly patients had significantly worse baseline mean HAQ-DI scores than younger patients, indicating greater disability. Patients with early and late-onset RA, regardless of age group, exhibited similar and rapid improvements in functional status and maintained their improvement in HAQ-DI throughout the open-label extension trials for up to a total of 6 years of etanercept therapy [29]. The effects of various immunosuppressive medications on the risk of cardiovascular events among a group of older patients with RA were investigated in Medicare beneficiaries (n = 3501). When compared with RA patients receiving only DMARD therapy, those receiving biologic immunosuppressive agents had neither an increased nor decreased risk of experiencing a cardiovascular event, whereas use of oral glucocorticoids and cytotoxic immunosuppressive agents other than MTX (azathioprine, cyclosporine and leflunomide) was associated with significant increases in the risk of cardiovascular events [30].

Other biologic agents

Anakinra

Anakinra is an interleukin-1 receptor antagonist. It is most commonly used in patients who are refractory to other treatments and are not good responders to TNF blockers. The overall magnitude of reductions in clinical symptoms and signs (20–30%) were relatively modest when compared with those reported in TNF-α-blocking agents (60–70%). Anakinra is not recommended to be used concomitantly with TNF blockers owing to an increased frequency of toxicity with such combinations. Injection-site reactions are the most frequently reported adverse event with anakinra [31].

Abatacept

Abatacept (CTLA4-Ig) is a fusion protein designed to modulate the T-cell costimulatory signal mediated through the CD28–CD80/86 pathway. It inhibits full activation of T cells. Clinical trials have provided evidence for the efficacy of abatacept in patients with active RA, despite prior treatment with mtx or anti-TNF therapies [32,33].

Rituximab

Rituximab is a chimeric monoclonal antibody to anti-CD20 that has been approved for the treatment of B-cell lymphoma since 1997. Rituximab causes selective and rapid depletion of the $CD20^+$ B-cell population. The first evidence of efficacy of rituximab in RA came from an open-label trial in a small number of patients who were treated with rituximab in conjunction with cyclophosphamide and high-dose steroids [34,35]. Consequent double-blind, placebo-controlled trials demonstrated that addition of rituximab to MTX appears to significantly reduce the signs and symptoms of RA and is relatively safe [36]. Rituximab has recently been approved for use in patients with RA who fail to respond to anti-TNF agents.

Despite the fact that patients under the age of 75 years were generally accepted in most of the clinical trials of these three biologic agents, initial evaluations did not include separate analyses of the effects of biologic agents on the elderly population.

In clinical practice, there has been a trend to treat earlier and more aggressively with DMARDs, combinations of DMARDs and biologic agents. As part of the overall increase in aggressiveness in therapy, along with growing safety experience with biologics and combination therapy, this should result in such approaches being utilized more commonly among the elderly population. In order to assess whether rheumatologists' treatment decisions were influenced by patients' age, 204 rheumatologists were questioned by a mail survey on two hypothetical scenarios that were identical except for the age of the patient. Rheumatologists were more likely to prefer aggressive DMARD treatment for the younger versus the older RA patient [37]. Treatment preferences of patients with RA for DMARDs were evaluated in a different study. Older patients with RA (mean 70 years of age) were initially given information about side effects, effectiveness and cost of MTX, gold, leflunomide and etanercept, and later they were asked to make preferences between these agents. Patients preferred etanercept over other treatment options [38]. In a study where EORA patients were matched with YORA patients based on their disease duration and

compared in order to assess the types of treatment measures used in the two groups, it was shown that EORA patients received biologic therapy and combination DMARD therapy less frequently than YORA patients, despite identical disease duration, and comparable disease severity and activity [39]. This suggests that there may be an underutilization of aggressive therapeutic regimens in the geriatric population. Although additional investigations are always welcome to help establish the potential hazards and benefits of the newer treatments in the elderly population, current experience suggests that efficacy and toxicity of rheumatologic drugs in the elderly population are comparable to younger adults.

Executive summary

Rheumatoid arthritis in the elderly: therapeutic interventions

- Adjunctive
  - Nonsteroidal anti-inflammatory drugs/cyclo-oxygenase-2 analgesics
- Glucocorticosteroids
- Disease-modifying antirheumatic drugs
  - Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, etc
- Biologics
  - Tumor necrosis factor inhibitors: etanercept, infliximab and adalimumab
  - Interleukin-1 inhibitor: anakinra
  - Cytotoxic T-lymphocyte antigen-4 immunoglobulin: abatacept
  - Anti-CD20 antibody: rituximab

Bibliography

1. Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC: Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States. Effect of different methods of case classification. *Arthritis Rheum.* 48, 917–926 (2003).
2. Deal CL, Meenan RD, Goldenberg DL *et al.*: The clinical features of elderly-onset rheumatoid arthritis. *Arthritis Rheum.* 28, 987–994 (1985).
3. Ferraccioli GF, Cavelieri F, Mercadanti M *et al.*: Clinical features, scintiscan characteristics and x-ray progression of late onset rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2, 157–161 (1984).
4. Glennas A, Tore KK, Oddvar A *et al.*: Recent onset arthritis in the elderly: a five year longitudinal observational study. *J. Rheumatol.* 27, 101–108 (2000).
5. van der Heijde DM, van Riel PL, van Leewen MA *et al.*: Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective follow-up study of early rheumatoid arthritis. *J. Rheumatol.* 18, 1285–1289 (1991).
6. van Schaardenburg D, Breedweld FC: Elderly-onset rheumatoid arthritis. *Semin. Arthritis Rheum.* 23(6), 367–378 (1994).
7. Kavanaugh AF: Rheumatoid arthritis in the elderly: is it a different disease? *Am. J. Med.* 103(6A), S40–S48 (1997).
8. Bijlsma JWJ: Analgesia and the patient with osteoarthritis. *Am. J. Ther.* 9, 189–197 (2002).
9. Rahme E, Marantette MA, Kong SX, Lelorier J: Use of NSAIDs, COX-2 inhibitors, and acetaminophen and associated coprescriptions of gastroprotective agents in an elderly population. *Arthritis Rheum.* 47(6), 595–602 (2002).
10. Whelton A, White WB, Bello AE *et al.*: Effects of celecoxib and rofecoxib on blood pressure and edema in patients 65 years of age or older with systemic hypertension and osteoarthritis. *Am. J. Cardiol.* 90(9), 959–963 (2002).
11. Bombardier C, Laine L, Reicin A *et al.*: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N. Engl. J. Med.* 343, 1520–1528 (2000).
12. Alsalameh S, Burian M, Mahr G, Woodcock BG, Geisslinger G: Review article: the pharmaceutical properties and clinical use of valdecoxib, a new cyclo-oxygenase-2-selective inhibitor. *Aliment. Phamacol. Ther.* 17, 489–501 (2003).
13. Healey LA, Sheets PK: The relation of polymyalgia rheumatica to rheumatoid arthritis. *J. Rheumatol.* 15, 750–752 (1988).
14. Lockie LM, Gomez E, Smith DM: Low-dose adrenocorticosteroids in the management of elderly patients with rheumatoid arthrtitis. *Semin. Arthritis Rheum.* 12, 373–381 (1983).
15. van Schaardenburg D, Valkeme R, Dijkmans BAC *et al.*: Prednisone for elderly-onset rheumatoid arthritis: efficacy and bone mass at one year. *Arthritis Rheum.* 36, S269 (1993).
16. Breedweld FC, Weisman MH, Kavanaugh AF *et al.*: The Premier study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate therapy. *Arthritis Rheum.* 54, 26–37 (2006).
17. Kremer JM, Genovese MC, Cannon GW *et al.*: Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. *Ann. Intern. Med.* 137, 726–733 (2002).
18. O'Dell JR, Haire CE, Erikson N: Treatment of rheumatoid arthritis with methotrexate sulfasalazine and hydroxychloroquine alone, or a combination of all three medications. *N. Engl. J. Med.* 334, 1287–1291 (1996).
19. Pincus T, Marcum SB, Callahan LF *et al.*: Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices. Second line drugs and prednisone. *J. Rheumatol.* 19, 1885–1894 (1992).
20. Wolfe F, Hawley DJ, Cathey MA: Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: a 14 year prospective evaluation of 1017 consecutive starts. *J. Rheumatol.* 17, 994–1002 (1990).

21. Maini R, St Clair EW, Breedweld F *et al.*: Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized Phase III trial. *Lancet* 354, 1932–1939 (1999).
22. Moreland LW, Baumgartner SW, Schiff MH *et al.*: Treatment of rheumatoid arthritis with a recombinant human tumour necrosis factor receptor (p75)-Fc fusion protein. *N. Engl. J. Med.* 337, 141–147 (1997).
23. Weisman MH, Moreland LW, Furst DE *et al.*: Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin. Ther.* 25(6), 1700–1721 (2003).
24. Lipsky PE, St Clair EW, van der Heijde *et al.*: Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N. Engl. J. Med.* 343, 1594–1602 (2000).
25. Genovese MC, Bathon JM, Martin R *et al.*: Etanercept versus methotrexate in patients with early rheumatoid arthritis: two year radiographic and clinical outcomes. *Arthritis Rheum.* 46, 1443–1450 (2002).
26. Keystone E, Kavanaugh A, Sharp J *et al.*: Adalimumab (D2E7), a fully human anti-TNFα monoclonal antibody, inhibits the progression of structural damage in patients with active rheumatoid arthritis despite concomitant methotrexate therapy. *Arthritis Rheum.* 46(Suppl. 9), S205 (2002) (Abstract 468).
27. Fleischman RM, Baumgartner SW, Tindall EA *et al.*: Response to etanercept (enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trials. *J. Rheumatol.* 30(4), 691–696 (2003).
28. 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, 234–243 (2006).
29. Schiff MH, Yu EB, Weinblatt ME *et al.*: Long-term experience in the treatment of rheumatoid arthritis in elderly and younger patients: patient-reported outcomes from multiple controlled and open-label extension studies. *Drugs Aging* 23, 167–178 (2006).
30. Solomon DH, Avorn J, Katz JN *et al.*: Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheum.* 54, 3790–3798 (2006).
31. Bresnihan B, Alvaro-Garcia JM, Cobby M *et al.*: Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum.* 41, 2196–2204 (1998).
32. Kremer JM, Westhovens R, Leon M *et al.*: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N. Engl. J. Med.* 20, 1907–1915 (2003).
33. Kremer JM, Genant HK, Moreland LW *et al.*: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144(12), 865–876 (2006).
34. Edwards JCW, Cambridge G: Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology* 40, 205–211 (2001).
35. Leonardo MJ, Edwards JCW, Cambridge G: Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Ann. Rheum. Dis.* 61, 883–888 (2002).
36. Edwards JCW, Szczepanski L, Szechinski J *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N. Engl. J. Med.* 350, 2572–2581 (2004).
37. Fraenkel L, Rabidou N, Dhar R: Are rheumatologists' treatment decisions influenced by patients' age? *Rheumatology* 45, 1555–1557 (2006).
38. Fraenkel L, Bogardus ST, Concato J, Felson DT, Wittink DR: Patient preferences for treatment of rheumatoid arthritis. *Ann. Rheum. Dis.* 11, 1372–1378 (2004).
39. Tutuncu ZN, Reed G, Kremer J, Kavanaugh A: Do patients with older onset rheumatoid arthritis patients receive less aggressive treatment than younger patients. *Ann. Rheum. Dis.* 65, 1226–1229 (2006).

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