possibility of recall bias. In fact, the mean dietary intake of vitamin D per day calculated in the present study tended to be high from the adequate intake (5 μg/day) published by the Ministry of Health and Welfare in Japan [37]. However, the Ministry of Health, Labour and Welfare in Japan also commented that the adequate intake had been determined as an index without enough scientific evidence. Simultaneously, this agency provided another index in which the tolerable upper intake level of vitamin D was 50 μg/day. Based on these issues regarding the estimation of vitamin D intake, we believe our results regarding the intake of vitamin D are not beyond the world consensus. Instead, the mean intake estimated in the present study could indicate that people in Japan have a much higher daily intake of vitamin D than those in most regions worldwide. Nonetheless, we were unable to conclude whether the total intake of vitamin D calculated in the present study represented actual values or was overestimated by using the questionnaire. In the other cohort from the urban area investigated in the ROAD study, we should be able to confirm the consistency of the estimation of vitamin D using the BDHQ questionnaire.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research B23390172 and B20390182 to NY, C20591737 to TA, and C20591774 to SM, for Young Scientists A18689031 to HO, and Collaborating Research with NSF 08033011–00262 (Director, NY) from the Ministry of Education, Culture, Sports, Science and Technology; and H17-Men-eki-009 (Director, KN), H18-Choujyu-037 (Director, TN), H20-Choujyu-009 (Director, NY), and H23-Chojyu-002 (Director, TA) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (NY, SM, HO, and TA), and research aid from the Japanese Orthopaedic Association (JOA-Subsidised Science Project Research 2006–1 and 2010–2, Director, HK). The authors wish to thank Dr. Takako Nojiri and Mr. Kazuhiro Hatanaka of the Gobo Public Health Centre; Dr. Naoki Hirabayashi of the Kawakami Clinic, Hidakagawa Town; Mrs. Tomoko Takijiri, Mrs. Kumiko Shinou, Mrs. Rie Takiguchi, Mrs. Kyoko Maeda, Ms. Ikuyo Ueyama, Mrs. Michiko Mori, Mrs. Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; Dr. Shinji Matsuda of the Shingu Public Health Centre; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, Mr. Shoichi Shimoichi, Mrs. Megumi Takino, Mrs. Shuko Okada, Mrs. Kazuyo Setoh, Mrs. Chise Ryouno, Mrs. Miki Shimosaki, Mrs. Chika Yamaguchi, Mrs. Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examinations. We also thank Ms. Kyoko Yoshimura, Mrs. Toki Sakurai, and Mrs. Saeko Sahara for their assistance with data reduction and administration.

Conflicts of interest None.

References

1. Lips P (2001) Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 22:477–501
2. Bischoff-Ferrari HA, Zhang Y, Kiel DP, Felson DT (2005) Positive association between serum 25-hydroxyvitamin D level and bone density in osteoarthritis. Arthritis Rheum 53:821–826
3. Rizzoli R, Bonjour JP (2004) Dietary protein and bone health. J Bone Miner Res 19:527–531
4. Bischoff-Ferrari HA, Willett WC, Orav EJ et al (2012) A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 367:40–49
5. Bischoff-Ferrari HA, Willett WC, Orav JE, Kiel DP, Dawson-Hughes B (2011) Fall prevention with vitamin D. BMJ 342:d2608
6. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J; IOF Committee of Scientific Advisors (CSA) Nutrition Working Group (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 20:1807–1820
7. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N (2010) IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 21:1151–1154
8. Lim SK, Kung AW, Sompongse S, Soontrapa S, Tsai KS (2008) Vitamin D inadequacy in postmenopausal women in eastern Asia. Curr Med Res Opin 24:99–106
9. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, Ragi-Eis S, Chandler J (2006) The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med 260:245–254
10. Nakamura K, Tsugawa N, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, Maruyama K, Oshiki R, Kobayashi R, Nashimoto M, Yoshihara A, Ozaki R, Okano T, Yamamoto M (2008) Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study. Bone 42:271–277
11. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, Yoshida H (2008) Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. J Bone Miner Res 23:1309–1317
12. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2010) Cohort Profile: research on osteoarthritis/osteoporosis against disability (ROAD) study. Int J Epidemiol 39:988–995
13. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Yoshida H, Suzuki T, Yamamoto S, Ishibashi H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628
14. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K (2005) Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study: a large observational study of the determinants of fracture in older men. Contemp Clin Trials 26:569–585
15. Sasaki S, Yanagibori R, Amano K (1998) Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 8:203–215
16. Hollis BW, Kamerud JQ, Selvaag SR, Lorenz JD, Napoli JL (1993) Determination of vitamin D status by radioimmunoassay with an 125I-labeled tracer. Clin Chem 39:529–533
17. Wahl DA, Cooper C, Ebeling PR, Eggersdorfer M, Hilger J, Hoffmann K, Josse R, Kanis JA, Mithal A, Pierroz DD, Stenmark J, Stöcklin E, Dawson-Hughes B (2012) A global representation of vitamin D status in healthy populations. Arch Osteoporo 7:155–172
18. Kellgren JH, Lawrence LS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16:494–502
19. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843. WHO, Geneva

20. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H, Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19(6):331–337
21. The Examination Committee of Criteria for Metabolic Syndrome (2005) The definition and criteria of metabolic syndrome. J Jpn Soc Intern Med 94:794–809, in Japanese
22. Ministry of Health, Labour and Welfare (2010) The outline of the results of National Health and Nutrition Survey 2010. http://www.mhlw.go.jp/stf/houdou/2r98520000020qbb-att/2r98520000021c0o.pdf (in Japanese). Accessed 28th Feb 2013
23. Japan Society of Nephrology (2009) Evidence-based practice guideline for the treatment of CKD. Clin Exp Nephrol 13:537–566
24. Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, Sarafin K, Poliquin S, Krieger J, Richards JB, Goltzman D, CaMos Research Group (2011) 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. Osteoporos Int 22(5):1389–1399. doi:10.1007/s00198-010-1362-7, Epub 2010 Aug 21
25. Japan Meteorological Agency (2012) http://www.data.jma.go.jp/obd/stats/etrn/view/nml_amd_ym.php?prec_no=65&block_no=1089&year=2012&month=&day=&view= and http://www.data.jma.go.jp/obd/stats/etrn/view/nml_sfc_ym.php?prec_no=65&block_no=47778&year=2012&month=&day=&view= (in Japanese). Accessed 28th Feb 2013
26. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B (1989) Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. N Engl J Med 321:1777–1783
27. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
28. Nashimoto M, Nakamura K, Matsuyama S, Hatakeyama M, Yamamoto M (2002) Hypovitaminosis D and hyperparathyroidism in physically inactive elderly Japanese living in nursing homes: relationship with age, sunlight exposure and activities of daily living. Aging Clin Exp Res 1:5–12
29. Lange NE, Sparrow D, Vokonas P, Litonjua AA (2012) Vitamin D deficiency, smoking, and lung function in the normative aging study. Am J Respir Crit Care Med 186(7):616–621. doi:10.1164/rccm.201110-1868OC, Epub 2012 Jul 19
30. Balsan S, Garabédian M (1991) Rickets, osteomalacia, and osteopetrosis. Curr Opin Rheumatol 3:496–502
31. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM (1998) Ultraviolet B and blood pressure. Lancet 352:709–710
32. Mathieu C, Gysemans C, Giulietti A, Bouillon R (2005) Vitamin D and diabetes. Diabetologia 48:1247–1257
33. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF (2007) Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med 32:210–216
34. Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC (2006) Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. Am J Prev Med 31:512–514
35. Holick MF (2006) Calcium plus vitamin D and the risk of colorectal cancer. N Engl J Med 354:2287–2288
36. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 296:2832–2838
37. Ministry of Health, Labour and Welfare (2009) Dietary Reference Intakes in Japan 2009. http://www.mhlw.go.jp/shingi/2009/05/s0529-4.html. Assessed on 28th Feb 2013

Bone 52 (2013) 516–523

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Risk factors for falls in a longitudinal population-based cohort study of Japanese men and women: The ROAD Study

Shigeyuki Muraki [a,*], Toru Akune [a], Yuyu Ishimoto [b], Keiji Nagata [b], Munehito Yoshida [b], Sakae Tanaka [c], Hiroyuki Oka [d], Hiroshi Kawaguchi [c], Kozo Nakamura [e], Noriko Yoshimura [d]

[a] Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Department of Orthopaedic Surgery, Wakayama Medical University, 811, Kimiidera, Wakayama-shi, Wakayama 641-8509, Japan
[c] Department of Sensory and Motor System Medicine, Faculty of Medicine, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[d] Department of Joint Disease Research, 22nd Century Medical and Research Center, Faculty of Medicine, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[e] Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, 4-1, Namiki, Tokorozawa-shi, Saitama 359-8555, Japan

ARTICLE INFO

Article history:
Received 20 April 2012
Revised 17 October 2012
Accepted 19 October 2012
Available online 24 October 2012

Edited by: Toshio Matsumoto

Keywords:
Falls
Longitudinal study
Pain
Osteoarthritis
Physical performance

ABSTRACT

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). A total of 452 men and 896 women were analyzed in the present study (mean age, 63.9 years). A questionnaire was used to assess the number of falls during the 3-year follow-up. Grip strength, 6-m walking time, and chair stand time were measured at baseline. Knee osteoarthritis (OA) and lumbar spondylosis were defined as Kellgren Lawrence = 2, 3 or 4. Vertebral fracture (VFx) was assessed with the Japanese Society of Bone and Mineral Research criteria. Osteoporosis was defined by bone mineral density using dual energy X-ray absorptiometry based on World Health Organization criteria. Knee and lower back pain were estimated by an interview. During a 3-year follow-up, 79 (17.4%) men and 216 (24.1%) women reported at least one fall, and 54 (11.9%) men and 111 (12.4%) women reported multiple falls. Knee pain was a risk factor for multiple falls in women, but not in men. VFx tended to be associated with multiple falls in women, but not in men. A longer 6-m walking time was a risk factor for multiple falls in women, whereas a longer chair stand time was a risk factor for multiple falls in men. We found gender differences in risk factors for falls.

Introduction

Falls are one of the main causes of injury, disability, and death among the elderly [1,2]. In Japan, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, falls and fractures are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living [3]. However, few population-based studies have been performed on the incidence of falls based on sex and age. Furthermore, in terms of factors associated with falls, muscle strength, balance, vision, functional capacities, and cognitive impairment are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures [4,5]. However, the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues because they cause chronic pain and disability [6,7]. The prevalence rates of radiographic knee OA and LS are 54.6% and 70.2%, respectively, in persons aged 40 years and older in Japan, which indicates that 25,300,000 and 37,900,000 persons aged 40 years and older are estimated to experience radiographic knee OA and LS, respectively [10]. The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require support with activities of daily living [3], but there have been few studies of the association between falls and OA [11,12]. In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain [13], but its correlation with the radiographic severity of knee OA is not as strong as expected [8]. In fact, in a study in Japan, approximately 20% of persons without knee OA had knee pain, and 30% of persons with severe knee OA had no knee pain [8]. Thus, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA [8]. Our previous study showed that knee pain is significantly associated with falls in women [14], but that study used a cross-sectional design; thus, a causal relationship remains unclear. Regarding LS, to the best of our knowledge, no population-based studies have been performed

* Corresponding author at: Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Fax: +81 3 5800 9179.
E-mail address: murakis-ort@h.u-tokyo.ac.jp (S. Muraki).

8756-3282/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bone.2012.10.020

regarding its association with falls except for our previous cross-sectional study [14], which showed that LS is not significantly associated with falls. In addition, among fractures due to osteoporosis (OP), vertebral fracture (VFx) is the most likely to lead to marked public health problems. VFx is reportedly associated with functional impairment [15], back pain, kyphosis [16,17], esophageal reflux [18], depressive mood [19], respiratory dysfunctions [20], and mortality [21]. However, whether VFx is an independent risk factor for the incidence of falls remains unclear.

Measuring walking speed is a simple way to assess health and function in older adults [22,23]. Walking speed has been found to be associated with falls in a few studies [4,24–26], although most studies were limited by a small sample size, a cross-sectional design [24,25], or evaluation of a single sex [4,26]. In addition, although walking abnormalities indicative by a slower walking speed are significantly associated with bone and joint diseases such as knee OA, LS, and their associated pain [14], no longitudinal studies have been performed to determine the associations of falls with bone and joint diseases and walking abnormalities at the same time. Furthermore, measuring the chair stand time is also reported to be a simple and established method to assess health and function in the elderly [27,28], but to the best of our knowledge, no longitudinal studies have been performed to determine the associations of falls with chair stand time.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls [12], indicating that single and multiple falls may have different backgrounds. Thus, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with the incidence of single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods

Participants

The ROAD study is a nationwide, prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OP and OA are the representative bone and joint diseases, respectively). ROAD consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [8–10,29]; a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.6 years) who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [30]. The participation rate was 75.6%. Participants in mountainous and coastal regions were also recruited from the resident registration lists, and the participation rates in these two areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Assessment of falls

Three years after the baseline data were obtained, we attempted to trace and review all 3,040 participants between 2008 and 2010; they were invited to attend a follow-up interview. All participants were interviewed with regard to falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 3-year follow-up, and if yes, how many falls did you experience"? At baseline, all participants were also interviewed regarding falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience"? According to a previous study on falls [31], a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment

All participants were interviewed by experienced orthopedists regarding knee pain and lower back pain at baseline and were asked the following questions based on previous studies [8,9]: "Have you experienced knee pain on most days in the past month, in addition to now"? and "Have you experienced lower back pain on most days in the past month, in addition to now"? Those who answered "yes" were defined as having pain. Buttock pain and sciatica were not included as lower back pain in the present study.

Radiographic assessment

At baseline, all participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot-map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. VFx was assessed by lateral radiographs of the lumbar spine (L1-L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria [32]. The films were marked up, and morphometric measurements of anterior, middle, and posterior heights on lateral radiography of the thoracic and lumbar spine were made. Wedge appearance was defined as a site at which the anterior height of the vertebra was $\leq$75% of the posterior height. Biconcave appearance occurred if the height of the central part of the vertebra was $\leq$80% of that of the anterior or posterior parts of the vertebra. Crush appearance occurred if the height of the anterior, central, and posterior parts of an axial vertebra were all reduced to $\leq$80% of the normal value (Supplementary Fig. 1). Knee and lumbar spine radiographs were also read without knowledge of the participant's clinical status by a single, experienced orthopedist (S.M.) using the Kellgren Lawrence (KL) radiographic atlas [33] to determine the severity of KL grading. Radiographs were scored as grade 0–4, with higher grades associated with more severe OA. We defined knee OA and LS as KL $\geq$2 in at least one knee and one intervertebral level, respectively. To evaluate the intraobserver variability of KL grading, 100 randomly selected radiographs of the knee and lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopedic surgeons (S.M. and H.O.) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Bone mineral density (BMD) measurement

BMD was measured at the lumbar spine (L2–4) and the proximal femur using dual energy X-ray absorptiometry (DXA) (Hologic

Discovery; Hologic, Waltham, MA, USA) at baseline. For quality control, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations at different regions. The BMD of the phantom was adjusted to 1.032 ± 0.016 g/cm^2 (± 1.5%) during all examinations. In addition, the same physician (N.Y.) examined all participants to prevent observer variability. Coefficient of variance (CV) for L2–L4 in the phantom was 0.35%, and CVs for L2–L4, the proximal femur, Ward's triangle, and the trochanter examined in five volunteers were 0.61–0.90, 1.02–2.57, 1.97–5.45, and 1.77–4.17%, respectively [34].

OP was defined based on World Health Organization (WHO) criteria in which OP was diagnosed as T-scores of BMD ≤2.5 standard deviations (SDs) lower than peak bone mass [35]. Mean L2–4 BMD (SD) for young adult men and women measured using the Hologic QDR devices in Japan is reportedly 1.011 g/cm^2 (0.119 g/cm^2) [36]. Mean femoral neck BMD (SD) in Japan is reported to be 0.863 g/cm^2 (0.127 g/cm^2) for young men and 0.787 (0.109) for young women [36]. The present study therefore defined OP using these indices as lumbar spine BMD <0.714 g/cm^2 for both men and women, and as femoral neck BMD <0.546 g/cm^2 for men and <0.515 g/cm^2 for women.

Physical performance

At baseline, anthropometric measurements were taken, including height and weight, and body mass index (BMI) (weight [kg]/height^2 [m^2]) was estimated based on the measured height and weight. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD, Saitama, Japan), and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded. Participants were told to walk from a marked starting line to a 6-m mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of two trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly persons [37]. The time taken for five consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al. [27] and used by other researchers [28]. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "Go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate [27].

Cognition assessment

At baseline, cognition was also evaluated for all participants using a Mini-Mental State Examination, and a cut-off score of <24 was used to select participants with cognitive impairment [38].

Statistical analyses

The differences in age and anthropometric measurements between the responders (those who completed the study) and non-responders (those lost to follow-up or who did not complete the study as described below) and between men and women were examined with a non-paired Student's *t*-test. Differences in physical performance measurements between the responders and non-responders and between men and women were examined with Wilcoxon signed-rank test. Differences in age and anthropometric measurements, among non-fallers, single fallers, and multiple fallers, were examined with one-way analysis of variance. Differences in physical performance measurements among non-fallers, single fallers, and multiple fallers were examined with the Kruskal–Wallis test. The prevalence of bone and joint diseases and cognitive impairment was compared between men and women and among non-fallers, single fallers, and multiple fallers with the chi square test. Multinomial logistic regression analysis after adjusting for age and BMI was used to determine the association of anthropometric measurements, physical performance, bone and joint diseases, and cognitive impairment with single and multiple falls compared with the absence of falls in men and women. Further, to determine an independent association of physical performance with single and multiple falls compared with the absence of falls, we used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory variables. To determine independent risk factors for single and multiple falls, we used multinomial logistic regression analysis with age, BMI, physical performance, bone and joint diseases, and cognitive impairment as explanatory variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1,690 participants in the mountainous and seaside cohorts at baseline in 2006 and 2007, 40 (2.4%) had died by the time of the review 3 years later, 97 (5.7%) did not participate in the follow-up study due to poor health, 16 (0.9%) had moved away, 51 (3.0%) declined the invitation to attend the follow-up study, and 47 (2.8%) did not participate in the follow-up study for other reasons. Among the 1,439 volunteers who did participate in the follow-up study, 68 (4.0%) provided incomplete fall questionnaires. In addition, six (0.4%) provided incomplete pain questionnaires; these were excluded. We also excluded eight (0.5%) participants who had undergone total knee arthroplasty before baseline. An additional nine (1.9%) participants did not perform the 6-m walking time or chair stand time, leaving a total of 1,348 (79.8%) participants (452 men and 896 women) from whom radiographs at baseline and complete fall and pain histories were obtained. The mean followup time was 2.93 ± 0.12 years, ranging from 2.65 to 3.22 years. Table 1 shows characterisctics of responders and non-responders. The responders were significantly younger than the non-responders (63.9 and 70.7 years, respectively). Physical performance measurements were better in responders than non-responders. Prevalence of knee OA, LS and knee pain was lower in responders (47.0, 61.6 and 9.7%,

Table 1
Baseline characteristics of responders and non-responders.

	Overall	Responders	Non-responders
Number of participants	1,690	1,348	342
Female (%)	64.7	66.5	57.9***
Age (years)	65.2 ± 12.0	63.9 ± 11.8	70.7 ± 11.4*
Height (cm)	155.2 ± 9.3	155.6 ± 9.0	153.6 ± 10.1*
Weight (kg)	55.6 ± 10.8	56.1 ± 10.7	53.7 ± 10.8*
BMI (kg/m^2)	23.0 ± 3.4	23.1 ± 3.4	22.7 ± 3.4
Grip strength (kg) (median [IQR])	26.0 [21.0–33.0]	26.0 [21.0–34.0]	24.0 [18.0–30.0]**
6-m walking time (s) (median [IQR])	5.0 [4.0–7.0]	5.0 [4.0–6.0]	7.0 [5.0–9.0]**
Chair stand time (s) (median [IQR])	9.0 [7.0–12.0]	9.0 [7.0–11.0]	12.0 [8.25–15.0]**
Cognitive impairment (%)	4.5	2.8	11.4***
Radiographic knee OA (%)	50.4	47.0	63.8***
Radiographic LS (%)	63.2	61.6	69.1***
Radiographic VFx	10.1	9.7	12.0
Knee pain (%)	24.3	22.2	32.6***
Lower back pain (%)	21.1	20.6	22.9
Previous falls (%)	17.3	16.3	21.0***

Values are mean ± SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. responders by non-paired Student's *t*-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

Table 2
Baseline characteristics of participants.

	Men	Women
Number of participants	452	896
Age (years)	64.9 ± 11.7	63.3 ± 11.8*
Height (cm)	164.0 ± 7.0	151.3 ± 6.6*
Weight (kg)	63.3 ± 10.7	52.5 ± 8.7*
BMI (kg/m^2)	23.5 ± 3.2	22.9 ± 3.4*
Grip strength (kg) (median [IQR])	37.0 [32.0–42.5]	23.5 [20.0–23.5]**
6-m walking time (s) (median [IQR])	5.0 [4.0–6.0]	5.0 [4.0–6.0]
Chair stand time (s) (median [IQR])	8.5 [7.0–11.0]	9.0 [7.0–11.0]
Cognitive impairment (%)	3.6	2.4
Radiographic knee OA (%)	37.4	51.9***
Radiographic LS (%)	76.1	54.2
Radiographic VFx	8.9	10.1
Knee pain (%)	15.3	25.7***
Lower back pain (%)	18.8	21.5
Previous falls (%)	13.1	18.0***

Values are mean ± SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. men by non-paired Student's t-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

respectively) than non-responders (63.8, 69.1 and 12.0, respectively). Prevalence of previous falls was significantly lower in responders than non-responders (16.3 and 21.0%, respectively).

Table 2 shows the age, anthropometric measurements, physical performance, and prevalence of cognitive impairment, bone and joint diseases, and previous falls of participants at baseline in men and women. Regarding physical performance, grip strength and chair stand time were significantly better in men (37.0 kg and 8.5 s, respectively) than in women (23.5 kg and 9.0 s, respectively), but the 6-m walking time was not (5.0 s and 5.0 s, respectively). The prevalence of radiographic knee OA and knee pain was significantly higher in women (51.9% and 25.7%, respectively) than in men (37.4% and 15.3%, respectively), whereas that of LS and lower back pain was not different between men and women. The prevalence of previous falls was significantly higher in women than in men (18.0% and 13.1%, respectively).

During the 3-year follow-up, 79 (17.4% [95% confidence interval [CI] 14.3–21.2]) men and 216 (24.1% [95% CI 21.4–27.0]) women reported at least one fall, and 54 (11.9% [95% CI 9.3–15.3]) men and 111 (12.4% [95% CI 10.4–14.7]) women reported multiple falls. The chi square test showed that the incidence of falls was significantly different between men and women ($p=0.0011$). The incidence of single and multiple falls was significantly higher in the mountainous regions (11.5% and 17.4%, respectively) than coastal regions (8.1% and 7.8%, respectively). With increasing age, the incidence of falls increased in women, but the incidence of falls was similar in men in their 60s and 70s (Fig. 1).

Table 3 shows the age, anthropometric measurements, physical performance, and BMD at baseline between non-fallers, single fallers, and multiple fallers. Age and BMI were significantly higher in female fallers than non-fallers, but this was not the case in men. Grip strength was worse in female fallers than non-fallers, but this was not the case in men. The 6-m walking time and chair stand time were longer in both male and female fallers than in non-fallers. LS and neck BMD were significantly lower in female fallers than non-fallers, but this was not the case in men.

We next examined the incidence rate of falls during the 3-year follow-up according to previous falls at baseline in men and women (Supplementary Fig. 2). The incidence rates of multiple falls were 7.9%, 22.7%, and 48.7% in men and 8.8%, 20.4%, and 43.1% in women among non-fallers, single fallers, and multiple fallers, respectively. The incidence rates of single falls were 5.9%, 9.1%, and 0.0% in men and 12.5%, 7.8%, and 8.6% in women among non-fallers, single fallers, and multiple fallers, respectively. The chi square test showed that the incidence of falls during the 3-year follow-up was significantly associated with previous falls at baseline in men and women ($p<0.0001$).

Fig. 2 shows the incidence rate of falls during the 3-year follow-up according to the presence of bone and joint diseases and cognitive impairment. The incidence rates of multiple falls were 16.6% and 9.2% in men and 14.8% and 9.7% in women in those with and without knee OA, respectively. The incidence rates of a single fall were 8.3% and 3.9% in men and 14.2% and 9.1% in women in those with and without knee OA, respectively. The chi square test showed that knee OA at baseline was significantly associated with the incidence rate of falls during the 3-year follow-up in men and women ($p<0.0001$). Regarding knee pain, the incidence rates of multiple falls were 18.8% and 10.7% in men and 18.7% and 10.2% in women in those with and without knee pain, respectively. The incidence rates of a single fall were 8.7% and 5.0% in men and 10.4% and 10.4% in women in those with and without knee OA, respectively. The chi square test showed that knee pain at baseline was significantly associated with the incidence of falls during the 3-year follow-up in men and women ($p<0.0001$). LS and lower back pain were not significantly associated with the incidence of falls in men ($p=0.52$ and 0.77, respectively) or in women ($p=0.45$ and 0.58, respectively). VFx at baseline was significantly associated with the incidence of falls in women (multiple falls 22.2% and 11.3%, single falls 14.4% and 11.4%, in those with and without VFx, respectively, $p=0.005$), but not in men ($p=0.06$). OP defined by L2–4 and femoral neck BMD was not associated with the incidence of falls in men and women. Cognitive impairment

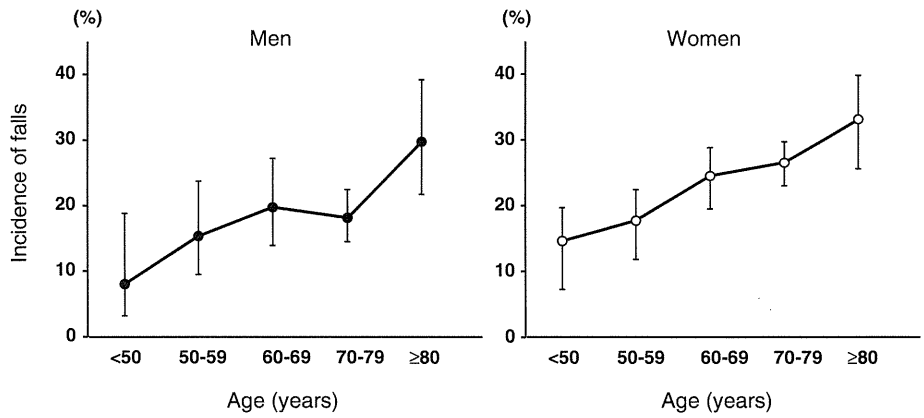

Fig. 1. Incidence rate of falls (error bars represent 95% confidence intervals) by gender and age strata.

Table 3
Comparison of characteristics among non-fallers, single fallers, and multiple fallers in men and women.

	Men				Women			
	Non-fallers	Single fallers	Multiple fallers	p value	Non-fallers	Single fallers	Multiple fallers	p value
Number of participants	373	25	54		680	105	111	
Age (years)	64.4 (11.7)	67.2 (13.2)	67.6 (10.1)	0.10	62.4 (11.6)	66.0 (12.6)	66.7 (11.4)	<0.001
BMI (kg/m^2)	23.4 (3.1)	24.6 (3.9)	23.7 (3.3)	0.16	22.8 (3.5)	22.7 (3.1)	23.8 (3.5)	0.01
Grip strength (kg) (median [IQR])	37.0 [32.0–43.0]	37.0 [30.0–41.5]	35.0 [28.8–40.0]	0.08	24.0 [20.0–27.0]	23.0 [19.5–27.0]	22.0 [18.0–26.0]	0.01
6-m walking time (s) (median [IQR])	4.5 [4.0–6.0]	5.5 [4.6–7.3]	6.2 [5.0–6.6]	<0.0001	5.0 [4.0–6.0]	5.0 [4.0–6.5]	5.5 [4.0–7.5]	<0.0001
Chair stand time (s) (median [IQR])	8.0 [7.0-10.0])	11.0 [9.0-12.0]	10.0 [8.0-13.0]	<0.0001	9.0 [7.0-11.0]	9.0 [8.0-12.0]	10.0 [8.0-12.25]	0.0001
LS BMD	1.05 (0.20)	1.05 (0.20)	1.05 (0.15)	0.99	0.89 (0.18)	0.85 (0.16)	0.86 (0.17)	0.04
Neck BMD	0.75 (0.13)	0.77 (0.12)	0.75 (0.10)	0.79	0.65 (0.13)	0.61 (0.11)	0.63 (0.11)	0.003

Values are the means (standard deviation), except where indicated.
One-way analysis of variance was used to determine the differences in age, height, weight and BMI among non-fallers, single fallers, and multiple fallers.
Kruskal–Wallis test was used to determine the differences in grip strength, 6-m walking time and chair stand time among non-fallers, single fallers, and multiple fallers.
The chi square test was used to determine the differences in the prevalence of cognitive impairment among non-fallers, single fallers, and multiple fallers.
BMI: body mass index, LS: lumbar spondylosis, BMD: bone mineral density.

was associated with the incidence of falls in men (multiple falls 31.3% and 10.9%, single falls 18.8% and 5.1%, in those with and without cognitive impairment, respectively, $p=0.002$), but not in women ($p=0.19$).

In men, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time, longer chair stand time, and previous falls were risk factors for falls, but grip strength, bone and joint diseases, and cognitive impairment were not

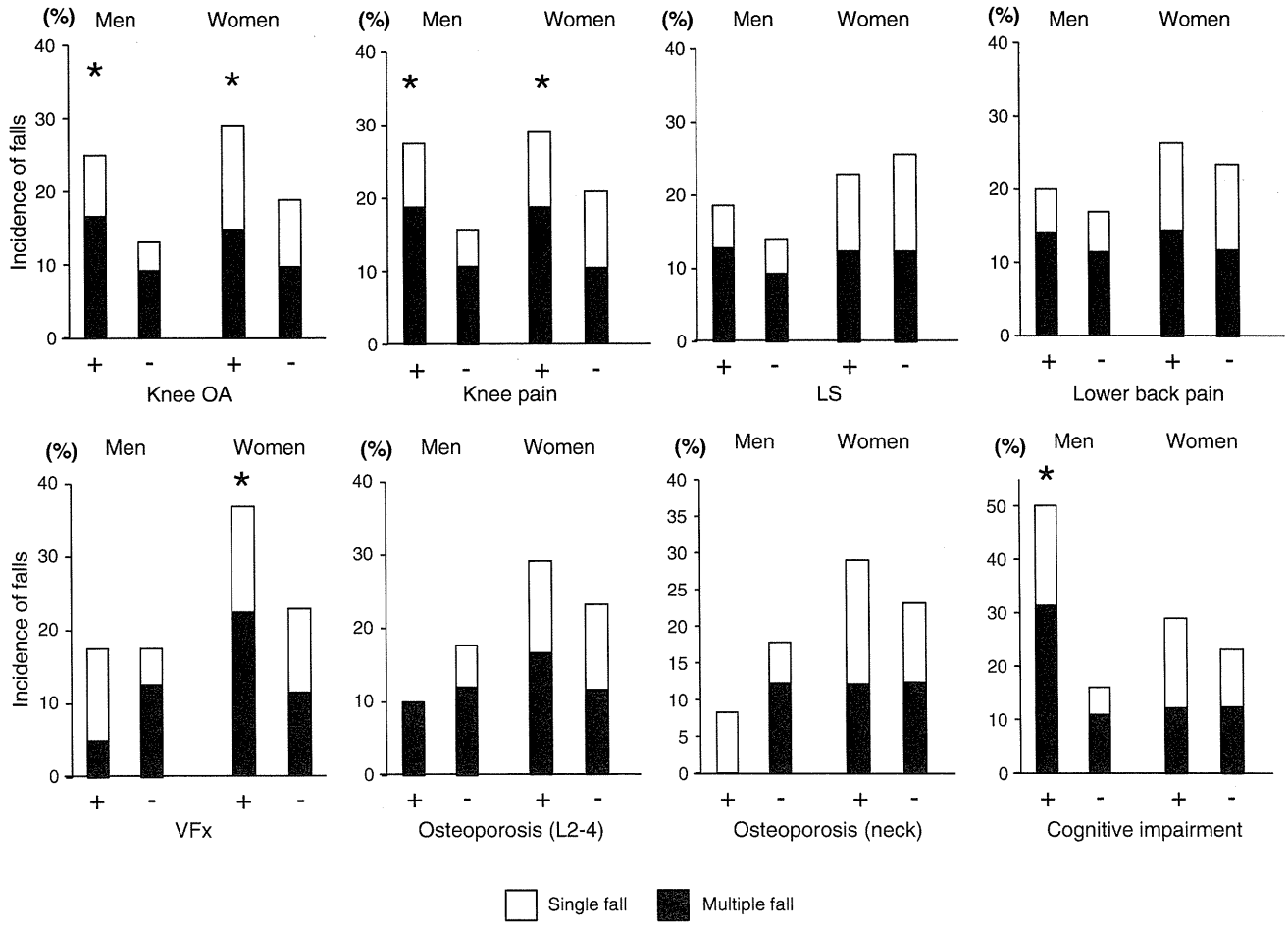

Fig. 2. Incidence of single and multiple falls by bone and joint diseases and cognitive impairment. *$p<0.05$ vs. participants without each disease or pain, respectively, according to the chi square test. OA, osteoarthritis; LS, lumbar spondylosis; VFx, vertebral fracture.

Table 4
Risk factors for single and multiple falls in men.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.90 (0.71–1.14)	0.84 (0.71–0.99)	1.14 (1.01–1.29)	0.88 (0.72–1.08)
6-m walking time (1 s increase)	1.12 (0.98–1.27)	1.13 (1.03–1.26)	1.11 (0.95–1.25)	1.11 (1.01–1.23)
Chair stand time (1 s increase)	1.17 (1.03–1.32)	1.21 (1.11–1.33)	1.15 (1.00–1.32)	1.21 (1.09–1.33)
LS BMD (0.1 mg/cm^2 increase)	1.00 (0.80–1.22)	1.00 (0.86–1.16)	0.92 (0.73–1.15)	0.97 (0.83–1.13)
Neck BMD (0.1 mg/cm^2 increase)	1.10 (0.81–1.47)	0.98 (0.78–1.21)	1.07 (0.73–1.51)	1.01 (0.77–1.30)
Knee OA	2.44 (1.09–5.56)	2.08 (1.18–3.70)	2.07 (0.84–5.21)	1.77 (0.95–3.33)
Knee pain	2.04 (0.72–5.09)	2.05 (0.99–4.00)	1.65 (0.57–4.21)	1.78 (0.85–3.55)
VFx	2.58 (0.82–6.85)	0.40 (0.06–1.36)	2.48 (0.75–7.04)	0.32 (0.05–1.13)
Cognitive impairment	6.19 (1.29–23.1)	4.83 (1.41–15.1)	13.48 (0.98–178.64)	3.17 (0.44–21.99)
Previous falls				
Single fall	–	–	–	3.52 (1.07–9.97)
Multiple falls	1.18 (0.25–4.61)	9.54 (3.15–30.08)	–	12.6 (5.80–27.97)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

(Table 4). Previous falls were significantly associated with the incidence of multiple falls. In women, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time was a risk factor for multiple, but not single falls (Table 5). Chair stand time also tended to be associated with the incidence of single and multiple falls. Regarding bone and joint diseases, knee pain was a risk factor for single and multiple falls. VFx also tended to be associated with multiple falls, but radiographic knee OA was not associated with falls. Cognitive impairment was a risk factor for multiple falls, but not for single falls. A history of previous falls was a risk factor for multiple, but not single falls.

To determine the independent association of each physical performance parameter with the incidence of falls, multinomial logistic regression analysis was performed with age, BMI, 6-m walking time, and chair stand time as explanatory variables. We found that a longer chair stand time was an independent risk factor for multiple falls (OR 1.18, 95% CI 1.06–1.32), but a longer 6-m walking time was not (OR 1.05, 0.93–1.16). In women, a longer 6-m walking time tended to be associated with the incidence of multiple falls (OR 1.09, 95% CI 0.98–1.22), but a longer chair stand time was not (OR 1.01, 95% CI 0.94–1.07). After adjusting for previous falls, the independent association of a longer chair stand time with the incidence of falls remained in men (OR 1.15, 95% CI 1.02–1.30), and the independent association of a longer 6-m walking time with the incidence of falls remained in women (OR 1.12, 95% CI 1.00–1.25). In addition, knee pain and cognitive impairment in women were also significantly associated with falls, and VFx tended to be associated with falls with multinomial logistic regression analysis after adjusting for age and BMI. Thus, to determine the independent association of physical performance, bone and joint diseases, and cognitive impairment, multinomial logistic regression analysis was used with age, BMI, 6-m walking time, knee pain, VFx, and cognitive impairment as explanatory variables. We found that a longer 6-m walking time was an independent risk factor for multiple falls (OR 1.08, 95% CI 1.00–1.18), but the significant association of knee pain, VFx, and cognitive impairment with the incidence of falls disappeared (OR 1.47, 95% CI 0.91–2.35, OR 1.52, 95% CI 0.80–2.81, and OR 1.16, 95% CI 0.35–3.24, respectively).

Discussion

The present study is the first longitudinal population-based cohort study to examine whether physical performance, bone and joint diseases, and cognitive impairment are risk factors for single and multiple falls in men and women. We found gender differences in risk factors for

Table 5
Risk factors for single and multiple falls in women.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.84 (0.70–0.99)	0.81 (0.68–0.95)	0.94 (0.77–1.11)	0.91 (0.75–1.08)
6-m walking time (1 s increase)	1.10 (1.01–1.19)	1.16 (1.08–1.25)	1.04 (0.94–1.14)	1.11 (1.02–1.20)
Chair stand time (1 s increase)	1.07 (1.02–1.12)	1.07 (1.03–1.12)	1.04 (0.99–1.10)	1.04 (0.99–1.09)
LS BMD (0.1 mg/cm^2 increase)	0.88 (0.78–1.00)	0.90 (0.80–1.01)	0.96 (0.83–1.11)	0.92 (0.80–1.06)
Neck BMD (0.1 mg/cm^2 increase)	0.75 (0.63–0.90)	0.85 (0.72–1.01)	0.79 (0.62–1.01)	0.87 (0.69–1.10)
Knee OA	1.79 (1.18–2.78)	1.75 (1.16–2.63)	1.52 (0.94–2.50)	1.12 (0.79–1.82)
Knee pain	1.83 (1.17–2.83)	2.22 (1.44–3.37)	1.62 (1.00–2.60)	1.60 (1.00–2.54)
VFx	1.54 (0.78–2.85)	2.40 (1.35–4.12)	1.15 (0.57–2.20)	1.81 (0.98–3.24)
Cognitive impairment	0.42 (0.02–2.12)	2.12 (0.68–5.60)	0.73 (0.19–2.61)	4.95 (1.50–16.08)
Previous falls				
Single fall	0.55 (0.16–1.74)	1.51 (0.33–5.41)	0.70 (0.30–1.43)	2.48 (1.40–4.28)
Multiple falls	0.86 (0.39–1.81)	8.55 (3.80–19.20)	1.06 (0.35–2.62)	6.93 (3.76–12.72)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

falls. Regarding physical performance, a longer chair stand time was an independent risk factor for falls in men, whereas a longer 6-m walking time was an independent risk factor for falls in women. Knee pain, VFx, and cognitive impairment were associated with falls in women, but not in men.

The present study is a population-based longitudinal study to determine whether bone and joint diseases are risk factors for falls in Japanese men and women. After adjusting for age and BMI, knee pain was a risk factor for falls in women, but not in men. The sex differences regarding the association of knee pain with falls may be partly explained by the weaker quadriceps muscles in women, which is known to be an independent risk factor for falls [16]. Muscle strength is higher in men than in women in all decades [39], which may obscure the association of knee pain with falls. In addition, given the insignificant association of radiographic knee OA with falls, falls may occur due to symptoms such as pain rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain is significantly associated with falls [11]. In other words, falls may be preventable when pain is relieved by medical care, even if patients have radiographic knee OA.

In the present study, LS and lower back pain were not associated with falls, whereas VFx was associated with falls. Lower BMD was not associated with falls in the present study, and thus, radiographic changes but not OP may be associated with falls. Studies of patients with VFx have reported increased kyphosis angles [16,17], which is an independent risk factor for injurious falls [40]. Previous studies [41,42] have demonstrated that people with kyphosis have greater balance abnormalities as assessed by computerized dynamic posturography. Specifically, they reported that women with OP-related kyphosis had greater mediolateral displacement and increased mediolateral velocity compared to controls [42]. In addition, lateral spontaneous sway amplitude has been reported to be the single best predictor of future risk of falls [43]. These observations may partly explain the association between VFx and falls.

In the present study, after adjusting for age and BMI, both a longer 6-m walking time and a longer chair stand time were associated with falls in men and women. A previous study also showed that slower walking speed is a risk factor for falls [44], although men and women were not separately analyzed in the study. To determine the independent association of the 6-m walking time and chair stand time, we further used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory factors, and found that in men, a longer chair stand time was an independent risk factor for multiple falls, but a longer 6-m walking time was not. In women, a longer 6-m walking time was associated with the incidence of multiple falls, whereas a longer chair stand time was not. This indicates that slower walking speed may more strongly affect the risk of falling in women than in men, whereas a longer chair stand time may more strongly affect the risk of falling in men than in women. The walking time and chair stand time can be easily and quickly measured in clinical and research settings without requiring monitoring devices or extensive training. The present study may indicate that walking time is a simple and quick option for measuring the risk of falling, particularly in women, and measuring the chair stand time is a simple and quick option for estimating the risk of falling, particularly in men.

The present study has several limitations. First, our participants lived in the community, and thus, our findings may not apply to elderly persons residing in institutions. Second, we did not include other anatomical locations of weight-bearing OA such as hip OA in the analysis, although this disorder also affects falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women [46], respectively, which is lower than that of KL=3 or 4 knee OA (12.2% and 21.0% in men and women, respectively) in the present study. Thus, it is possible that hip OA would not strongly affect the results of the present study. Third, non-responders were older, had lower physical performance and higher prevalence of knee pain, which were risk factors for falls. This means that the incidence of falls in the present study may have been underestimated. Fourth, the accuracy and reliability of recall of falls over the past 3 years was not assessed in the present study. Previous studies have shown that 13–32% of elderly subjects with confirmed falls did not recall falling over a 12-month period [47], even when excluding subjects with cognitive impairment. Therefore, the incidence of falls may be underestimated, particularly in older subjects and those with cognitive impairment. In addition, individuals are more likely to recall a fall that resulted in injury, which may have influenced the results of this study.

Conclusion

The present longitudinal analysis using a large-scale population from the ROAD study revealed gender differences in risk factors for falls. A longer walking time was a risk factor for falls in women, whereas a longer chair stand time was a risk factor for falls in men. Knee pain and VFx were risk factors for falls in women, but not in men. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of bone and joint diseases and their relationship with falls.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (S19109007, MB20390182, C20591737, C20591774), Young Scientists (A18689031), and Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology; H17-Men-eki-009, H18-Choujyu-037, H20-Choujyu-009, H21-Chouju-Wakate-011, and H22-Chouju-Wakate-007 from the Ministry of Health, Labour and Welfare; Research Aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006–1 and 2010-2); and Grant No. 166 from the Japan Orthopaedics and Traumatology Foundation.

The authors thank Tomoko Takijiri and other members of the Public Office in Hidakagawa Town, and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji Town, for their assistance in the location and scheduling of participants for examinations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bone.2012.10.020.

References

[1] Baker S, O'Neill B, Karpf RS. The Injury Fact Book. Lexington, Mass: Lexington Books; 1984.
[2] Fife D, Barancik JI, Chatterjee MS. Northeastern Ohio Trauma Study, II: injury rates by age, sex and cause. Am J Public Health 1984;74:473-8.
[3] Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2007. http://www.mhlw.go.jp/toukei/list/20-19-1.html.
[4] Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 1996;348:145-9.
[5] Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701-7.
[6] Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3–26.
[7] Emery SE, Ringus VM. Osteoarthritis of the spine. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 427-52.
[8] Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137-43.

[9] Muraki S, Oka H, Mabuchi A, Akune T, En-yo Y, Yoshida M, et al. Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study. Ann Rheum Dis 2009;68:1401-6.
[10] Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). J Bone Miner Metab 2009;27:620-8.
[11] Arden NK, Crozier S, Smith H, Anderson F, Edwards C, Raphael H, et al. Knee pain, knee osteoarthritis, and the risk of fracture. Arthritis Rheum 2006;55:610-5.
[12] Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. JAMA 1989;261:2663-8.
[13] Linaker CH, Walker-Bone K, Palmer K, Cooper C. Frequency and impact of regional musculoskeletal disorders. Baillieres Clin Rheumatol 1999;13:197-215.
[14] Muraki S, Akune T, Oka H, En-yo Y, Yoshida M, Nakamura K, et al. Prevalence of falls and its association with knee osteoarthritis and lumbar spondylosis as well as knee and lower back pain in Japanese men and women. Arthritis Care Res 2011;63:1425-31.
[15] Burger H, Van Daele PL, Grashuis K, Hofman A, Grobbee DE, Schutte HE, et al. Vertebral deformities and functional impairment in men and women. J Bone Miner Res 1997;12:152-7.
[16] Ross PD. Clinical consequences of vertebral fractures. Am J Med 1997;103: 30S-42S [discussion 42S-43S].
[17] Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998;128:793-800.
[18] Yamaguchi T, Sugimoto T, Yamada H, Kanzawa M, Yano S, Yamauchi M, et al. The presence and severity of vertebral fractures is associated with the presence of esophageal hiatal hernia in postmenopausal women. Osteoporos Int 2002;13:331-6.
[19] Gold DT, Lyles KW, Shipp KM, Drezner MK. Osteoporosis and its nonskeletal consequences: their impact on treatment decisions. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis. 2nd ed. San Diego, California, USA: Academic Press; 2001. p. 819-29.
[20] Leech JA, Dulberg C, Kellie S, Pattee L, Gay J. Relationship of lung function to severity of osteoporosis in women. Am Rev Respir Dis 1990;141:68-71.
[21] Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int 2004;15:38-42.
[22] Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003;51: 314-22.
[23] Cesari M, Kritchevsky SB, Penninx BW, Nicklas BJ, Simonsick EM, Newman AB, et al. Prognostic value of usual gait speed in well-functioning older people — results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:1675-80.
[24] Lipsitz LA, Jonsson PV, Kelley MM, Koestner JS. Causes and correlates of recurrent falls in ambulatory frail elderly. J Gerontol 1991;46:M114-22.
[25] Wolfson L, Whipple R, Amerman P, Tobin JN. Gait assessment in the elderly: a gait abnormality rating scale and its relation to falls. J Gerontol 1990;45:M12-9.
[26] Chan BK, Marshall LM, Winters KM, Faulkner KA, Schwartz AV, Orwoll ES. Incident fall risk and physical activity and physical performance among older men: the Osteoporotic Fractures in Men Study. Am J Epidemiol 2007;165:696-703.
[27] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.
[28] Bohannon RW. Sit-to-stand test for measuring performance of lower extremity muscles. Percept Mot Skills 1995;80:163-6.
[29] Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) Study. Int J Epidemiol 2010;39:988-95.
[30] Shimada H, Lord SR, Yoshida H, Kim H, Suzuki T. Predictors of cessation of regular leisure-time physical activity in community-dwelling elderly people. Gerontology 2007;53:293-7.
[31] Tinetti M, Baker D, Dutcher J. Reducing the risk of falls among older adults in the community. Berkeley, CA: Peacable Kingdom Press; 1997.
[32] Inoue T. Clinical features and findings: osteoporosis. Bone 1990;4:39-47 [in Japanese].
[33] Kellgren JH, Lawrence JS, editors. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs of Arthritis. Oxford: Blackwell Scientific; 1963.
[34] Yoshimura N, Kakimoto T, Nishioka M, Kishi T, Iwasaki H, Niwa T, et al. Evaluation of reproducibility of bone mineral density measured by dual energy X-ray absorptiometry (DPX-L). J Wakayama Med Soc 1997;48:461-6.
[35] World Health Organizaion. Assessment og fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series, 843. Geneva: WHO; 1994.
[36] Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, et al. Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 2001;19:331-7.
[37] Steffan TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling older people: six-minute walk test, Berg balance scale, timed up and go test, and gait speeds. Phys Ther 2002;82:128-37.
[38] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189-98.
[39] Sinaki M, Nwaogwugwu NC, Phillips BE, Mokri MP. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil 2001;80:330-8.
[40] Kado DM, Huang MH, Nguyen CB, Barrett-Connor E, Greendale GA. Hyperkyphotic posture and risk of injurious falls in older persons: the Rancho Bernardo Study. J Gerontol A Biol Sci Med Sci 2007;62:652-7.
[41] Lynn SG, Sinaki M, Westerlind KC. Balance characteristics of persons with osteoporosis. Arch Phys Med Rehabil 1997;78:273-7.
[42] Sinaki M, Brey RH, Hughes CA, Larson DR, Kaufman KR. Balance disorder and increased risk of falls in osteoporosis and kyphosis: significance of kyphotic posture and muscle strength. Osteoporos Int 2005;16:1004-10.
[43] Maki BE, Holliday PJ, Topper AK. A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. J Gerontol Med Sci 1994;49:M72-84.
[44] Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. J Gerontol 2009;64:896-901.
[45] Arden NK, Nevitt MC, Lane NE, Gore LR, Hochberg MC, Scott JC, et al. Osteoarthritis and risk of falls, rates of bone loss, and osteoporotic fractures. Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1999;42:1378-85.
[46] Inoue K, Wicart P, Kawasaki T, Huang J, Ushiyama T, Hukuda S. Prevalence of hip osteoarthritis and acetabular dysplasia in French and Japanese adults. Rheumatology (Oxford) 2000;39:745-8.
[47] Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc 1988;36:613-6.

SUPPLEMENT

Next stage of RA treatment: is TNF inhibitor-free remission a possible treatment goal?

Yoshiya Tanaka

The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Correspondence to
Professor Yoshiya Tanaka, The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, 1-1 Iseigaoka, Kitakyushu 807-8555, Japan; tanaka@med.uoeh-u.ac.jp

Received 12 July 2012
Accepted 11 September 2012
Published Online First 19 December 2012

ABSTRACT

Biological agents targeting tumour necrosis factor (TNF) have revolutionised the treatment of rheumatoid arthritis (RA) and clinical remission has become a realistic treatment goal. Discontinuing anti-TNF therapy after sustained remission has emerged as an important area of investigation in rheumatology from the risk-benefit point of view, including health economic considerations. However, there is little information as to whether 'biologic-free remission' is possible after sustained remission following intensive treatment with TNF inhibitors in RA. European studies such as BeSt and OPTIMA in patients with early RA and Japanese studies such as remission induction by remicade in patients with RA and HONOR in patients with long-standing RA encountered during routine clinical practice have shown that, after a reduction in disease activity to clinical remission or low disease activity by infliximab or adalimumab in combination with methotrexate, patients can successfully remain in clinical remission without TNF inhibitors with no radiological and functional damage progression of articular destruction. Experimental findings in TNF-deficient mouse models suggest that TNF inhibitors may change the disease process of RA and bring about the potential of immunological remission, raising the possibility of a 'treatment holiday' of TNF inhibitors after intensive treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality.[1–4] It is recommended that the treatment of RA is initiated with monotherapy or a combination of disease-modifying antirheumatic drugs (DMARDs).[5–8] Patients with active RA, however, are often resistant to DMARD therapy, especially in the context of structural progression. Thus, biological agents targeting proinflammatory cytokines such as tumour necrosis factor (TNF), which plays a pivotal role in the pathological processes of RA leading to joint destruction, have been developed. The combined use of biological agents targeting TNF and methotrexate (MTX) has revolutionised the treatment of RA, producing significant improvements in clinical, structural and functional outcomes that were not previously observed. Accordingly, the concept of treating RA to target by employing a composite measure of disease activity is generally being accepted worldwide.[5] Clinical remission is perceived as an appropriate and realistic primary goal in many patients while, in those with long-standing RA, low disease activity is the aim.

After the induction of clinical remission by combination therapy with TNF inhibitors and MTX, it has to be maintained as described in No. 8 of the 'Treat-to-Target', which leads to structural remission and functional remission.[5] Caution is needed when deciding to reduce or discontinue treatment with synthetic DMARDs because stopping DMARDs in remission was followed by twice as many flare-ups, difficulties in reintroducing remission and a halt in damage, whereas similar studies are not available for the biological agents.[5] However, because of the economic burden associated with expensive biological products and the long-term safety by inhibiting a particular cytokine, the possibility of discontinuation of biological products after the maintenance of remission needs to considered. Thus, treatment strategies with TNF inhibitors targeting induction and/or maintenance of clinical remission can potentially lead to subsequent discontinuation of the TNF inhibitors. However, there is no well-established firm evidence that remission can be sustained even if a biological agent is discontinued (ie, 'biologic-free remission'). In this paper we discuss whether the discontinuation of TNF inhibitors such as adalimumab and infliximab is possible in patients with RA after achieving low disease activity or clinical remission during a certain period with TNF inhibitors.

IS DISCONTINUATION OF ADALIMUMAB POSSIBLE AFTER SUSTAINED REMISSION?

Clinical remission has recently become an achievable goal by the combination therapy of TNF inhibitors and MTX in many patients, and appropriate induction of remission is a prerequisite to halt joint damage and functional disabilities, which revealed improved outcomes with strategic therapeutic approaches.[4–8] If a patient is in persistent remission after tapering of glucocorticoids, one can consider tapering TNF inhibitors, especially if this treatment is combined with DMARDs. However, there is little information about the characteristics of patients with long-standing RA in whom adalimumab can be successfully discontinued.

We have carried out a study (Humira discontinuation without functional and radiographic damage progressiON follOwing sustained Remission, HONOR) to investigate whether adalimumab-free remission is maintained after discontinuation of adalimumab in Japanese patients with established RA in sustained remission obtained with adalimumab plus MTX.[9] In this study, sustained remission

was defined as a persistent Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate (ESR) of < 2.6 for at least 6 months. Informed consent was obtained from patients aged >18 years who had attained sustained remission with adalimumab plus MTX to discontinue adalimumab and those followed up for >6 months were evaluated. The primary endpoint was the proportion of patients who maintained sustained remission for at least another 6 months after discontinuation. DAS28, simplified disease activity index (SDAI), clinical DAI, health assessment questionnaire-disability index (HAQ-DI) and yearly progression of the modified total Sharp score (ΔmTSS) were assessed before and after discontinuation of adalimumab. To predict retaining adalimumab even after withdrawing it, a logistic regression and receiver-operating characteristic analysis were conducted on clinical variables and cut-off values at discontinuation were determined.

Of the 197 patients who started adalimumab treatment between July 2008 and April 2011 in our department, 69 (35.0%) met the criteria for sustained remission and 51 consented to enter the study. The mean age of the 51 patients was 59.5 years and mean disease duration was 7.1 years, indicating that the population included patients with long-established disease. The mean DAS28-ESR score was 5.1, implying that most patients had active disease despite MTX. Furthermore, because the mean ΔmTSS was 11.5, the addition of TNF inhibitors to MTX was needed to control joint destruction as well as disease activity. Fifty-eight percent of the evaluable 50 patients maintained adalimumab-free remission at 6 months. DAS28-ESR at discontinuation was found significantly to predict the retention of remission with a cut-off value of 2.16. Most patients (94.9%) showed no evidence of radiographic progression (ΔmTSS ≤ 0.5) at 1 year. Moreover, HAQ-DI observed at the time of adalimumab discontinuation was almost preserved at 6 months. Therefore, although the sample size is limited, the results of the HONOR study indicated that, after reaching remission with adalimumab plus MTX, most patients could discontinue adalimumab for more than 6 months without disease flare, functional impairment and radiographic damage progression. Also, deep remission at discontinuation was associated with successful biologic-free remission.

Recently, a multinational double-blind randomised controlled study was performed to determine the optimal protocol for treatment initiation with adalimumab plus MTX in patients with early RA (OPTIMA).[10] Outcomes of withdrawal or continuation of adalimumab were assessed in patients who achieved a stable low disease activity target after 26 weeks of initially assigned treatment with adalimumab and MTX. Of the 466 patients with RA treated with adalimumab plus MTX, 207 (44%) achieved stable low disease activity and were re-randomised to placebo or adalimumab plus MTX. At week 78, 86% and 66% of patients treated with adalimumab plus MTX and placebo plus MTX, respectively, achieved DAS28 remission (<2.6). SDAI remission and ΔmTSS remission were comparable for both groups.

Another trial conducted in Germany (HIT HARD) addressed the question of whether early induction therapy with a subsequent step-down strategy leads to a long-term clinical effect in patients with recent onset RA compared with initial and continued MTX monotherapy.[11] During the first 24 weeks, 172 patients were treated with adalimumab or placebo plus MTX and, after week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase 47.9% of patients treated with MTX plus adalimumab achieved DAS28 remission and, at week 48, 42.4% were still in remission with 24 weeks of adalimumab-free treatment.

In the OPTIMA and HIT HARD trials, early induction therapy with adalimumab and MTX followed by withdrawal of adalimumab led to a loss of the response gained with the initial combination treatment in a subgroup of patients, but not in all patients. Unlike the HONOR study, among patients with early RA such as those in both studies, some might be capable of comprehensive disease control with initial and continued MTX monotherapy. However, the results of the HONOR study indicate that a 'treatment holiday' of biological agents by discontinuing adalimumab is now feasible in patients with RA following sustained remission, even in patients with long-standing RA encountered during routine clinical practice (figure 1).

IS DISCONTINUATION OF INFLIXIMAB POSSIBLE AFTER SUSTAINED LOW DISEASE ACTIVITY?

We also conducted a study (Remission induction by Remicade in RA patients, RRR) to examine the possibility of biologic-free remission or low disease activity in patients with RA whose mean disease duration was 5.9 years.[12] This study included a total of 114 patients with RA from 26 centres. The mean DAS28-ESR score was 5.6, implying that most patients had active disease despite MTX therapy. Furthermore, because the mean ΔmTSS was approximately 14, the addition of TNF inhibitors to MTX was needed to control disease activity and joint destruction. The patients enrolled in the study were those who had reached and maintained low disease activity (DAS28<3.2) for more than 24 weeks with infliximab treatment and who then agreed to discontinue the treatment. Among the 102 evaluable patients who completed the study, 56 (55%) maintained low disease activity after 1 year and showed no progression in radiological damage and functional disturbance, and 44 (43%) remained in clinical remission (DAS28<2.6). The mean disease duration of the group who achieved remission or low disease activity in the RRR study was 4.8±5.9 years, which made this study the first to prove that patients with long disease duration may also aim for discontinuation. Furthermore, ΔmTSS≤0.5 was observed in 67% and the HAQ-DI score was only 0.174 in patients who maintained a low disease activity for 1 year after discontinuation. We therefore conclude that more than half of patients who maintain a low disease state for more than 24 weeks on infliximab can discontinue infliximab and maintain low disease activity for a year without radiographic or functional disease progression.

The possibility of biologic-free remission in patients with RA was initially reported by a TNF20 study.[13] The combination of infliximab and MTX in patients with early RA who had symptoms for <12 months provided tight control of the disease activity. Although infliximab was withdrawn at 1 year, low clinical activity and functional abilities were sustained for another year. In the Netherlands, the Behandelstrategieën (BeSt) study was conducted to compare four treatment strategies and to observe clinical outcomes in patients with early RA (disease duration <2 years after onset, mean disease duration 0.8 years).[14–16] In this study, 508 patients with high disease activity were allocated to four groups and evaluated by DAS44 every 3 months. In patients with DAS44>2.4 (intermediate or high disease activity) a change or addition of medications was required, in those with DAS44≤2.4 (remission or low disease activity) the current medication was continued and, in patients with DAS44≤2.4 continued over 6 months, concomitant medications including infliximab were decreased and/or discontinued. In the fourth group who started infliximab, 90 of 120 patients (75%) achieved DAS44≤2.4 and

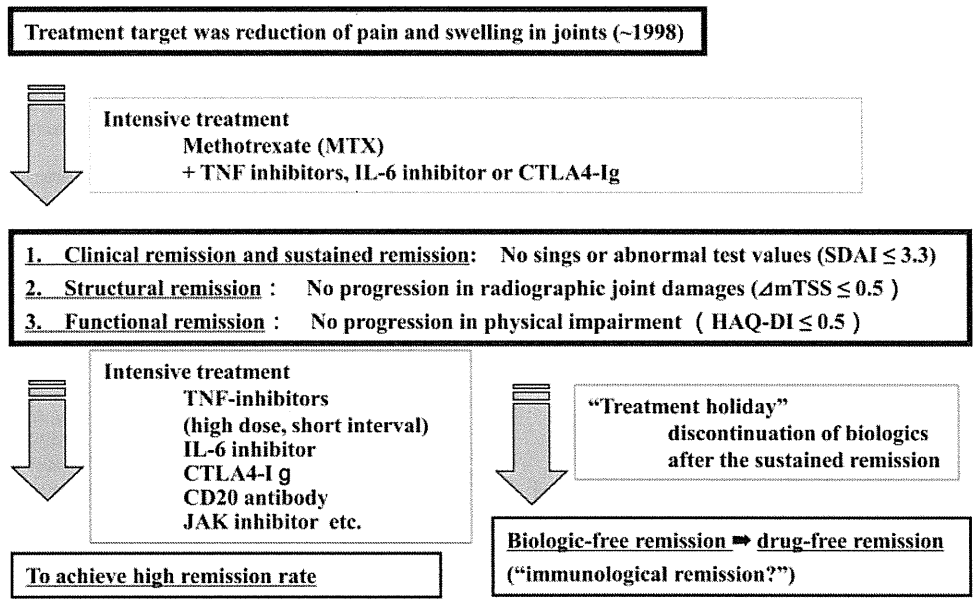

Figure 1 The next stage of the treatment of rheumatoid arthritis: intensive treatment and the possibility of a 'treatment holiday'. IL, interleukin; TNF, tumour necrosis factor.

infliximab was withdrawn in 77 cases because DAS44≤2.4 was maintained for 6 months. In the fourth group started with MTX and infliximab, the total cost of work loss and medical expenses was less than half that of the other groups started with DMARDs.

The biggest difference between the patient populations in the RRR and BeSt studies was disease duration (mean disease duration 0.8 years in the BeSt study vs 5.9 years in the RRR study), implying that biologic-free remission is possible in patients with early onset RA and also in those with long-established disease. It remains unclear whether discontinuation of biological agents targeting TNF is beneficial for comorbidity such as increased cardiovascular and/or cerebrovascular events. Since nearly a decade has passed since the BeSt study was initiated, some answers to this query may be drawn from the study.

IS TNF INVOLVED IN THE DISEASE PROCESSES?

In the BeSt study, 58% of 120 patients discontinued infliximab and 19% of patients have discontinued all DMARDs and remained in clinical remission with minimal joint damage progression 5 years after receiving infliximab and MTX as initial treatment for RA, suggesting the possibility of treatment-free remission.

In our institution, among 577 patients who were treated with infliximab, 88 patients reached biologic-free remission and only five are currently in drug-free remission without MTX. Although both TNF inhibitors and MTX play a role in the treatment, our data suggest that discontinuation of MTX appears to be difficult in patients with long-established RA. The mode of action of MTX is not discussed here, but its continuation is needed as a standard key drug. Discontinuation of biological agents benefits the economic burden of long-term management.

Accumulated studies indicate the involvement of TNF in the disease process in animal arthritis models, especially at the early stages of joint inflammation. Introduction of TNF transgene into the mouse results in typical polyarthritis, with hyperplasia of the synovium, inflammatory infiltrates in the joint space, pannus formation and cartilage and bone destruction. However, the polyarthritis and joint destruction obtained were completely ameliorated by the preventive as well as curative application of TNF inhibitors.[17] Meanwhile, TNF deficiency reduced the incidence of autoimmune arthritis in most models.[18–20] For instance, K/BxN is a model of arthritis which expresses both T cell receptor (TCR) transgene *KRN* and the MHC class II molecule *Ag7*. In the mouse, TCR recognises a self-antigen glucose-6-phosphate isomerase (GPI) and produces anti-GPI antibody, and arthritis is induced by the injection of the serum to naïve mice. Although TNF is highly expressed in K/BxN mice, deficiency of the *TNF* gene markedly reduced both the incidence and severity of the autoimmune arthritis. SKG is also an inflammatory arthritis model with a point mutation of *ZAP-70*, a member of spleen tyrosine kinase (Syk) associated with the TCRζ chain. The knockout mutation of the *TNF* gene in SKG mice showed amelioration of both the incidence and the severity of the arthritis.

If animal data partially reflect the efficacy of TNF inhibitors in patients with RA, it suggests that TNF inhibitors may change the disease course or induce immunological remission in RA. Interestingly, 48% of the 577 patients with RA described became negative for rheumatoid factor (RF) when infliximab was discontinued, although 77% of them were positive for RF at baseline when infliximab was initiated. Although the studies are limited, when the disease course is successfully changed by intensive treatment including the combination of MTX and TNF inhibitors, patients with RA may have the possibility of a 'treatment holiday' of TNF inhibitors.

CONCLUSIONS

Although the studies are limited, after reduction of disease activity to clinical remission by TNF inhibitors such as infliximab and adalimumab in combination with MTX, patients may be able to discontinue TNF inhibitors without clinical flare, radiographic progression of articular destruction and functional impairment. A 'treatment holiday' of biological agents is possible in patients with early RA and also in those with long-established RA. It has to be realised that intensive treatment with a TNF inhibitor is required to bring about the 'treatment

holiday' efficiently since deep remission was a major factor affecting the success of discontinuation of TNF inhibitors in two Japanese studies. Discontinuation of biological agents during treatment of RA has become an important area of investigation in rheumatology patients and governments from the risk-benefit viewpoint including health economic considerations. Meanwhile, because treatment with TNF inhibitors can bring about the induction of remission, sustained remission and subsequent biologic-free remission—that is, it may change or modify the course of the disease—a clinical and basic research approach to the 'process-driven disease course' of RA is warranted from wider standpoints, leading to the elucidation of pathological mechanisms and treatment strategies.

Acknowledgements The author thanks all medical staff in all institutions for providing the data.

Funding The series of studies were also supported in part by a Research Grant-In-Aid for Scientific Research by the Ministry of Health, Labor and Welfare of Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan and the University of Occupational and Environmental Health, Japan.

Competing interests YT has received consulting fees, speaking fees and/or honoraria from Mitsubishi-Tanabe Pharma Corporation, Abbott Japan, Eisai, Chugai Pharmaceutical, Janssen Pharmaceutical, Santen Pharmaceutical, Pfizer Japan, Astellas Pharma, Daiichi-Sankyo, GlaxoSmithKline, Astra-Zeneca, Otsuka Pharmaceutical, Actelion Pharmaceuticals Japan, Eli Lilly Japan, Nippon Kayaku, UCB Japan, Quintiles Transnational Japan, Ono Pharmaceutical and Novartis Pharma and has received research grants from Bristol-Myers Squibb, MSD, Chugai Pharmaceutical, Mitsubishi-Tanabe Pharma Corporation, Astellas Pharma, Abbott Japan, Eisai and Janssen Pharmaceutical.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1. **Scott DL,** Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;**376**:1094–108.
2. **McInnes IB,** Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;**365**:2205–19.
3. **Redlich K,** Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discovery* 2010;**11**:234–50.
4. **Tanaka Y.** Intensive treatment and treatment holiday of TNF-inhibitors in rheumatoid arthritis. *Curr Opin Rheumatol* 2012;**24**:319–26.
5. **Smolen JS,** Aletaha D, Bijlsma JWJ, *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;**69**:631–7.
6. **Felson DT,** Smolen JS, Wells G, *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;**70**:404–13.
7. **Schoels M,** Knevel R, Aletaha D, *et al*. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis* 2010;**69**:638–43.
8. **Singh JA,** Furst DE, Bharat A, *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;**64**:625–39.
9. **Tanaka Y,** Hirata S, Nawata M, *et al*. Discontinuation of adalimumab without functional and structural progress after attaining remission in patients with rheumatoid arthritis (an interim report of HONOR study) (abstract), ACR2011, #2468.
10. **Kavanaugh A,** Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;**72**:64–71.
11. **Detert J,** Bastian H, Listing J, *et al*. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naïve patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis*. Published Online First 27 June 2012. doi:10.1136/annrheumdis-2012-201612.
12. **Tanaka Y,** Takeuchi T, Mimori T, *et al*. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis, RRR (remission induction by remicade in RA) study. *Ann Rheum Dis* 2010;**69**:1286–91.
13. **Quinn MA,** Conaghan PG, O'Connor PJ, *et al*. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;**52**:27–35.
14. **Goekoop-Ruiterman YPM,** de Vries-Bouwstra JK, Allaart CF, *et al*. Clinical and radiographic outcomes of four different strategies in patients with early rheumatoid arthritis (the BeSt study). A randomized controlled trial. *Arthritis Rheum* 2005;**52**:3381–90.
15. **Goekoop-Ruiterman YP,** de Vries-Bouwstra JK, Allaart CF, *et al*. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2008;**58**(2 Suppl):S126–35.
16. **van der Bijl AE,** Goekoop-Ruiterman YP, de Vries-Bouwstra JK, *et al*. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:2129–34.
17. **Herrak P,** Görtz B, Hayer S, *et al*. Zoledronic acid protects against local and systemic bone loss in tumor necrosis factor-mediated arthritis. *Arthritis Rheum* 2004;**50**:2327–37.
18. **Ji H,** Pettit A, Ohmura K, *et al*. Critical roles for interleukin 1 and tumor necrosis factor alpha in antibody-induced arthritis. *J Exp Med* 2002;**196**:77–85.
19. **Hata H,** Sakaguchi N, Yoshitomi H, *et al*. Distinct contribution of IL-6, TNF-alpha, IL-1, and IL-10 to T cell-mediated spontaneous autoimmune arthritis in mice. *J Clin Invest* 2004;**114**:582–8.
20. **Sakaguchi S,** Benham H, Cope AP, *et al*. T-cell receptor signaling and the pathogenesis of autoimmune arthritis: insights from mouse and man. *Immunol Cell Biol* 2012;**90**:277–87.

Next stage of RA treatment: is TNF inhibitor-free remission a possible treatment goal?

Yoshiya Tanaka

Ann Rheum Dis 2013 72: ii124-ii127 originally published online December 19, 2012
doi: 10.1136/annrheumdis-2012-202350

OPEN ACCESS

EXTENDED REPORT

Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions

Josef S Smolen,[1,2] Monika M Schoels,[2] Norihiro Nishimoto,[3] Ferdinand C Breedveld,[4] Gerd R Burmester,[5] Maxime Dougados,[6] Paul Emery,[7] Gianfranco Ferraccioli,[8] Cem Gabay,[9] Allan Gibofsky,[10] Juan Jesus Gomez-Reino,[11] Graeme Jones,[12] Tore K Kvien,[13] Miho Murakami,[3] Neil Betteridge,[14] Clifton O Bingham III,[15] Vivian Bykerk,[9] Ernest H Choy,[16] Bernard Combe,[17] Maurizio Cutolo,[18] Winfried Graninger,[19] Angel Lanas,[20] Emilio Martin-Mola,[21] Carlomaurizio Montecucco,[22] Mikkel Ostergaard,[23] Karel Pavelka,[24] Andrea Rubbert-Roth,[25] Naveed Sattar,[26] Marieke Scholte-Voshaar,[27] Yoshiya Tanaka,[28] Michael Trauner,[29] Gabriele Valentini,[30] Kevin L Winthrop,[31] Maarten de Wit,[32] Désirée van der Heijde[4]

For numbered affiliations see end of article.

Correspondence to
Professor Josef S Smolen, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Waehringer Guertel 18–20, Vienna A-1090, Austria; josef.smolen@wienkav.at; josef.smolen@meduniwien.ac.at

Accepted 21 October 2012
Published Online First 21 November 2012

ABSTRACT

Background Since approval of tocilizumab (TCZ) for treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA), interleukin 6 (IL-6) pathway inhibition was evaluated in trials of TCZ and other agents targeting the IL-6 receptor and ligand in various RA populations and other inflammatory diseases. This consensus document informs on interference with the IL-6 pathway based on evidence and expert opinion.

Methods Preparation of this document involved international experts in RA treatment and RA patients. A systematic literature search was performed that focused on TCZ and other IL6-pathway inhibitors in RA and other diseases. Subsequently, incorporating available published evidence and expert opinion, the steering committee and a broader expert committee (both including RA patients) formulated the current consensus statement.

Results The consensus statement covers use of TCZ as combination- or monotherapy in various RA populations and includes clinical, functional and structural aspects. The statement also addresses the second approved indication in Europe JIA and non-approved indications. Also early phase trials involving additional agents that target the IL-6 receptor or IL-6 were evaluated. Safety concerns, including haematological, hepatic and metabolic issues as well as infections, are addressed likewise.

Conclusions The consensus statement identifies points to consider when using TCZ, regarding indications, contraindications, screening, dose, comedication, response evaluation and safety. The document is aimed at supporting clinicians and informing patients, administrators and payers on opportunities and limitations of IL-6 pathway inhibition.

SCOPE AND PURPOSE

The treatment of rheumatoid arthritis (RA) has significantly advanced over the past decade with the recent optimisation of the use of synthetic disease modifying anti-rheumatic drugs (sDMARDs), such as methotrexate (MTX),[1 2] newly developed sDMARDs, such as leflunomide,[3 4] and with the addition of biological DMARDs (bDMARDs) to the RA therapeutic armamentarium. The first bDMARDs studied and subsequently approved were inhibitors of tumour necrosis factor (TNFi),[5 6] followed by abatacept, an inhibitor of T-cell costimulation,[7] rituximab, an agent leading to B-cell depletion[8] and tocilizumab (TCZ), an interleukin 6 (IL-6) receptor blocker. Although there is little direct comparison data between the five currently approved TNFi (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) or other bDMARDs, reviews and meta-analyses of clinical trial data suggest these compounds have similar efficacy.[9–12] They differ in terms of molecular structures (chimeric, humanised or human monoclonal antibodies, or recombinant receptor constructs), route of application (intravenous or subcutaneous), and adverse event profiles, with these differences determined by the agents' modes of action. In contrast to bDMARDs, the modes of action of sDMARDs are generally not well-understood, their adverse event profiles are mostly different and their costs are substantially lower.

Given the variety of available therapies and in light of the variability discussed above, recommendations for the management of RA have been developed.[13 14] However, these recommendations, despite their sophisticated and quite comprehensive nature, capture only parts of the complexity of the application of individual drugs. Therefore, consensus statements on the use of groups of agents or individual classes of agents have been developed, providing pertinent information for various stakeholders.[15 16] Developing recommendations for individual classes of drugs may bear the value of

providing more detailed information on a particular agent than can usually be offered by more general presentations. This is especially true for describing the safety aspects of certain therapeutics, but can also be true for deliberations with regard to efficacy.

In the present manuscript, inhibition of the effects of IL-6 was the focal point of a consensus activity. Interference with IL-6 is currently possible by using TCZ, a humanised monoclonal antibody directed against the IL-6 receptor (IL-6-R), but other compounds, such as another antibody targeting the IL-6R and several agents focusing on the cytokine IL-6 itself, are currently in development.[17–20]

An international group of experts and patient representatives experienced in clinical research, the use of biological agents and the development of consensus statements and treatment recommendations, convened in Vienna in March 2012 to develop a consensus statement on the current use of IL-6 pathway inhibition in rheumatology. This statement targets primarily those health professionals who prescribe IL-6 inhibition related therapies, health professionals who do not primarily prescribe the agent but care for patients treated with TCZ, as well as patients interested in information on IL-6R or IL-6 inhibition. In addition, this document may also be informative to payers, hospital managers, administrators and other stakeholders interested in treating RA and other chronic inflammatory diseases.

The consensus statement will address the following areas:

- Background on IL-6 and mode of action of TCZ and other compounds
- Indication, considerations and screening for initiating TCZ in RA
  - Treatment dose algorithm and co-medication
  - Evaluation of response and management of response
  - Predictive factors of response
  - Contraindications and adverse events
  - Long-term exposure—efficacy and safety issues
- Patient perspectives
- Research agenda

To achieve these objectives, a systematic literature review (SLR) of the published literature on the efficacy and safety of TCZ and steering other biologicals inhibiting the IL-6 pathway in patients with RA was first undertaken to identify relevant data, which also included abstracts of recent international conferences, such as the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) meetings of 2011 and abstracts known to be submitted to EULAR 2012 to be used and referenced if accepted for presentation. The results of this SLR[21] were presented to and discussed by the committee, providing the basis for the discussions of the large task force and the conclusions that will be presented herein. Levels of evidence will be indicated next to each recommendation, in line with published guidelines (see also online supplement).[22]

BACKGROUND

IL-6 is a small polypeptide of approximately 26 kD molecular weight that is involved in the differentiation and growth of a variety of cells.[23 24] It has originally been described as B-cell stimulating factor, hepatocyte stimulating factor and interferon β2, before it was cloned[23 24] and shown that all these activities were attributable to a single molecule which did not convey antiviral actions. IL-6 binds to a receptor (IL-6R), which consists of the actual cytokine binding part, the IL-6Rα chain, and a second moiety, gp130, which transduces the respective signals into the cell. A number of recent reviews have covered its mode of action and related aspects in detail, and the reader is referred to these and similar publications.[23–27] More detailed insights are also summarised in the online supplementary files.

TCZ, a humanised anti-IL-6R antibody directed to the IL-6Rα chain, is currently the only IL-6 pathway inhibitor licensed for the treatment of RA, and the evidence available on safety and efficacy therefore rests almost exclusively on information related to this agent. However, other IL-6 inhibiting therapies are currently in development and phase 2 data already partly available; this information is also included in our analysis.

MODE OF ACTION

Inhibition of the effects of IL-6 has been primarily studied in a number of phase II and III clinical trials of TCZ. The original designation of the antibody was myeloma receptor antibody, since IL-6 is a growth factor for myeloma cells. TCZ showed initial clinical efficacy in collagen-induced arthritis in monkeys;[28] in a rare lymphoproliferative disorder, Castleman's disease;[29 30] and also in early phase evaluations in RA.[29 31–34] Its effects on acute phase reactant (APR) levels and other features of chronic inflammation are fully in line with inhibition of the above-mentioned modes of action of IL-6. However, it is currently unknown if cells to which an anti-IL-6R antibody binds, are lysed, undergo apoptosis, are ingested by phagocytes of the spleen or others, or simply circulate with their receptor being blocked. It is also unknown if binding of such antibodies to the receptors might lead to cap formation and subsequent ingestion of the IL-6R. These questions need to be addressed as part of the research agenda.

RECOMMENDATION FOR THE USE OF TCZ

Indication, considerations and screening for initiating TCZ in RA

Indication

Adult RA

In line with the current licensed indication in Europe, TCZ may be used in adult patients with active RA, normally with at least moderate disease activity according to a validated composite measure, who have had an inadequate response to, or intolerance of at least one synthetic DMARD and/or TNF-inhibitor.[35]

Before concluding that a patient has not sufficiently responded to a previous synthetic DMARD or a TNF-blocker, attempts should be made to improve the ongoing regimen by optimising the respective DMARD or TNF-blocker dose, if indicated, considering pertinent recommendations.[14]

TCZ fulfilled the requirements for the above indications as a consequence of the results of several clinical trials (level 1a, grade A). In table 1A, the response rates according to the ACR improvement criteria[36] as observed in phase III clinical trials are depicted, showing superiority to control arms in all studies. A significant decrease in the disease activity score using 28 joint counts (DAS28) and high proportions of EULAR moderate and good response as well as DAS28 remission (DAS28<2.6) rates have been observed. However, interpretation of the LATTER data is impeded by the high weight of the APR component in the DAS28 formula[37 38] and the prominent effect of IL-6 inhibition on the hepatic APR production, which can lead to exaggerated improvement or response rates when this measure is employed. Nevertheless, the pre-eminent requirement of improvement in both swollen and tender joints to fulfil ACR improvement criteria[36] and the published clinical trial data showing a decrease in disease activity across all variables studied as well as functional improvement and structural

Table 1A ACR20, 50 and 70% response rates (% of patients fulfilling improvement criteria) and percentage of HAQ change from baseline or fulfilment of HAQ-MCID (reduction of more than 0.22) in different clinical trials of TCZ

FU	Study	% of patients fulfilling ACR20	% of patients fulfilling ACR50	% of patients fulfilling ACR70	HAQ-decrease from baseline (%)	Comment
TCZ combination therapy						
16 weeks	CHARISMA[33] 7 arms, escalating doses of TCZ monotherapy (2 vs 4 vs 8 mg/kg) versus each dose in combination with MTX Results for 8 mg/kg combination therapy versus MTX	74/41	53/29	37/16		MTX-IR
24 weeks	OPTION[40] PL/TCZ 4/TCZ 8 mg/kg	26/48/59	11/31/44	2/12/22	21/33/34	MTX-IR
	TOWARD[41] PL/TCZ 8 mg/kg	25/61	9/38	3/21	13/33*	MTX/DMARD-IR†
	RADIATE[42] PL/TCZ 4/TCZ 8 mg/kg	10/30/50	4/17/29	1/5/12	0/18/23	Anti-TNF-IR
	ROSE[43] PL vs TCZ 8 mg/kg		11/30			DMARD-IR†
52 weeks	LITHE[44]‡ PL/TCZ 4/TCZ 8 mg/kg	25/47/56*	10/29/36*	4/16/20*	26/35/39*	MTX-IR
TCZ monotherapy						
12 weeks	Japanese[34] PL/TCZ 4 vs 8 mg/kg	11/57/78	2/26/40	0/20/16		DMARD-IR
16 weeks	CHARISMA 7 arms, escalating doses of TCZ monotherapy (2 vs 4 vs 8 mg/kg) versus each dose in combination with MTX Results for 8 mg/kg monotherapy vs MTX	63/41	41/29	16/16		MTX-IR
24 weeks	AMBITION[45] MTX/TCZ 8 mg/kg	53/70	34/44	15/28	33/44	
	ACT-RAY[46 47] TCZ 8 mg/kg/TCZ 8 mg/kg +MTX	70/72	40/46	25/25	33/33*,§	MTX-IR, switch to vs adding TCZ; LDA and DAS28-REM were more frequent on combination than TCZ mono-therapy
	SATORI[48] MTX/TCZ 8 mg/kg	25/80	11/49	6/30	25/50*	MTX-IR
	ADACTA,[49] TCZ 8 mg/kg/ adalimumab 40 mg	65/49	47/28	33/18	n.a.	Adalimumab monotherapy
52 weeks	SAMURAI[50] DMARDs/TCZ 8 mg/kg	34/78	13/64	6/44	10/50*	DMARD-IR
Other IL-6 or IL-6R inhibitors (phase II; week 12)						
12 weeks	*Anti-IL-6R*					
	Sarilumab[20 51] PL/150 mg	46/72	n.a.	n.a.	n.a.	
	Anti-IL-6					
	BMS945429[19] PL/active	36/82¶	15/50	6/43	29/39	
	Sirukumab[17] PL/active	30/63¶	3/27	n.a.	n.a.	
	Olokizumab[18]	n.a.	n.a.	n.a.	n.a.	

*Estimated values using baseline data and approximate values from respective curves, since exact data not provided in the publications.
†DMARDs aside from MTX: sulfasalazine, leflunomide, antimalarials and other.
‡1 year data.
§Differences between groups in ACT-RAY not significant; all other studies showed significant differences from control; where studied, 4 mg/kg dose was also significantly different from control; details see individual publications.
¶Highest response rate among several arms.
ACR, American College of Rheumatology; DMARDs, disease modifying antirheumatic drugs; DAS-28, disease activity score using 28 joint counts; FU, weeks of follow-up; HAQ, Health Assessment questionnaire disability index; IR, insufficient response; LDA, low disease activity; MCID, minimally clinically important difference; MTX, methotrexate; n.a., not available; PL, placebo; TCZ, tocilizumab; TNF, tumour necrosis factor; for trial acronyms see respective publications.

effects (table 1B), provide evidence that TCZ is an effective biological disease modifying drug. Indeed, when focusing on the clinical disease activity index (CDAI), a score that does not comprise an APR in its formula, TCZ remains significantly effective.[39] Its efficacy appears to be of similar magnitude as that of TNF-inhibitors, abatacept and rituximab.[9]

TCZ has shown superior efficacy compared with control groups in the treatment of RA manifestations in combination with MTX and other sDMARDs; TCZ was assessed mostly in combination with MTX, but in some studies up to 20% of the patients received other sDMARDs like leflunomide, sulfasalazine and/or chloroquine/hydroxychloroquine without noticeable differences in efficacy.[41 52] TCZ was also effective as monotherapy. Studies of other biologicals employed as monotherapy mostly revealed similar efficacy as MTX and had generally less efficacy than combination therapy.[10 12 14] By contrast, TCZ monotherapy has been shown in Japanese and an international trial to convey significantly better efficacy compared with MTX (in MTX naïve or MTX never failed patients) or other DMARDs in clinical, functional and, in the SAMURAI trial, also structural respects, although it should be borne in mind that in the Japanese studies MTX was dosed at only 8 mg weekly (level 1b, grade A; table 1A).[45 48 50] A recent trial comparing TCZ monotherapy with adalimumab monotherapy (ADACTA trial) revealed clinical superiority of TCZ.[49] While this finding is not surprising given the fact that adalimumab monotherapy was not shown to be clinically superior to MTX monotherapy in early RA[53] (and TCZ monotherapy was not compared with a combination of ADA+MTX), the data implicitly confirm the previous findings on the efficacy of TCZ monotherapy compared with DMARDs studied hitherto.[45 48 50] For monotherapy, the 8 mg/kg dose is the only one studied in phase 3 trials.

Adding TCZ to MTX (combination therapy) compared with switching from MTX to TCZ monotherapy (withdrawal of MTX) failed to convey superior clinical and structural effects in

Table 1B Radiographic changes in TCZ clinical trials assessing joint damage

Study	Placebo+MTX	4 mg/kg+MTX	8 mg/kg+MTX	8 mg/kg mono-therapy	DMARDs	Assessment
LITHE†[44]	1.13	0.34*	0.29*			GTSS, mean change from baseline
SAMURAI†[50]				2.3 (1.5–3.2)**	6.1 (4.2–8.0)	vdH-TSS, mean (95%CI) change from baseline
ACT-RAY†[46]			0.08 (1.88)	0.22*** (1.11)		Change of GTSS at 6 months; mean (SD)
ACT-RAY†[47]			92.4%	85.5%****		No radiographic progression at 1 year

*p<0.0001; **p<0.001; ***p=0.26; ****p=0.007; using as a cutoff the smallest detectable change of the Genant modified Sharp score of 1.5 (a relatively high value as a cutoff for non-progression; data on lower values, such as 0 or 0.25 are awaited).
†The LITHE and SAMURAI data, including p values, relate to 1 year study results; for ACT-RAY, data shown reflect 6-month analyses which showed no significant differences between TCZ monotherapy and combination with MTX.
DMARDs, disease modifying antirheumatic drugs; GTSS, Genant-modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab; vdH-TSS, van der Heijde modified total Sharp score.

patients with established RA and active disease despite MTX treatment for most endpoints (ACT-RAY trial; table 1A).[46] Thus, these data further imply that monotherapy is effective and is not significantly inferior to combination therapy. However, many of the assessments showed better numerical outcomes in the combination therapy; moreover, at 6 months and 12 months, significantly more patients achieved DAS28 low disease activity or remission, respectively, and less patients had progression of joint damage on combination therapy compared with monotherapy.[47] Thus, while TCZ monotherapy is superior to MTX monotherapy, a number of patients may benefit from the combination more than from switching to monotherapy. However, if combination with MTX or other DMARDs is contraindicated and monotherapy with a biological agent is mandated, TCZ should be considered. In light of all of the above aspects, a 3-arm trial comparing MTX, TCZ and the combination in early RA is still awaited to clarify these questions.

Throughout all studies assessing a 4 mg/kg and an 8 mg/kg dose in combination with MTX, both doses had significantly better efficacy than control regarding clinical functional and structural outcomes,[44 40 42] but there was a consistent (though statistically not significant) clinical superiority of the higher dose (table 1A), which was particularly prominent for more profound levels of efficacy (eg, ACR70) and in patients who have failed TNFi; these data suggest that many patients receiving TCZ at 4 mg/kg will have only a limited, inadequate response and a majority no profound response (level 1c, grade A). Trials investigating an increase to 8 mg/kg after a starting dose of 4 mg/kg, as currently recommended in the US, have not been systematically performed, although in the clinical trials evaluating the 4 mg/kg dose, rescue therapy with 8 mg/kg had been implemented in patients who did not achieve at least 20% improvement in tender and swollen joint counts by week 16;[44 40 42] moreover, in a post-hoc analysis TNFi-insufficient responders (IR) and MTX-IR patients not achieving an adequate response to TCZ 4 mg/kg by week 16 showed improvement after escalation to 8 mg/kg.[54] Importantly, the rate of anaphylactic reactions appears to be several fold higher at the 4 mg/kg than at the 8 mg dose of TCZ (see below).[55] A lower dose than 4 mg/kg is not recommended because of its insufficient efficacy and even higher risk of immunogenicity.[33] In general, based on the available data, the task force felt that starting combination therapy with a dose of 8 mg/kg and possibly decreasing the dose when necessitated by adverse events may be more appropriate than starting at 4 mg/kg due to the better efficacy and lesser immunogenicity of the higher dose; clinical and laboratory monitoring is necessary at either dose.

TCZ has also shown significant effects on retarding progression of joint damage, both in combination as well as monotherapy;[50 46 44] structural efficacy was observed at both 4 mg/kg and 8 mg/kg, where studied (table 1B). Moreover, TCZ inhibited x-ray progression in patients with low as well as persistent high clinical disease activity, thus dissociating the tight link between disease activity and joint damage, as also seen with TNF-blockers.[56] TCZ is effective across all populations investigated, that is, established and early RA; MTX-naïve,[45] DMARD-IR[33 41 52 48 46 44 40] and TNFi-IR[42] patients (level 1a to 1b, grade A). No differences in efficacy were seen between patients positive or negative for rheumatoid factor.[52 57]

In line with its mode of action, TCZ leads to a rapid reduction in APR, including C-reactive protein (CRP) levels, which is sustained at the 8 mg/kg dose; in contrast, with 4 mg/kg CRP decreases are not maintained throughout the 4 week time course and this saw tooth pattern suggests an inadequate suppression of the pathway at this dose.[41 44 40 42] Further, TCZ leads to an increase in haemoglobin levels, especially in RA patients with anaemia, presumably by inhibiting the production of hepcidin, a molecule stimulated by IL-6 and involved in the pathways to anaemia of chronic disease;[58] it may be thus useful in RA patients with otherwise refractory anaemia of chronic disease. The adverse event profile will be discussed in detail in subsequent sections.

Considerations for initiating treatment

Before starting any treatment for RA in general and thus also TCZ, an individual therapeutic goal should be determined as a shared decision between the patient and the treating physician, who should be experienced in the diagnosis and treatment of RA as well as the use of biological therapies and their complications[14 59] (level 5, grade D). Several studies have shown that RA patients cared for by physicians experienced in the management of their disease, thus primarily rheumatologists, have better outcomes than those followed by less specialised physicians.[60 61] Patients to whom the rheumatologist suggests treatment with TCZ should have at least moderate disease activity by composite scores, such as the DAS28 (>3.2), the Simplified or CDAI (SDAI>11; CDAI>10) or similar scores[62] (level 5, grade D). A raised CRP is also preferable.

In the phase III trials, TCZ was started in patients with an inadequate response to sDMARDs[41 44 40] or also TNFi.[42] TCZ was used in combination with sDMARDs, primarily MTX, or as monotherapy.[33 45 50 46 44] When TNFi preceded TCZ therapy, requirements for time of discontinuation were different among prior agents: for etanercept it was at least 2 weeks, while for adalimumab and infliximab at least 8 weeks.[42] In an open label phase IV study, TCZ therapy was used within 1 month of stopping TNFi without any increases in serious infections or other safety signals.[63] In clinical practice it is likely that TCZ will be frequently applied earlier than after such intervals; however there are no available data supporting the safety of TCZ in such cases.[64] Of note, TCZ has not yet

been studied in patients who had been previously exposed to rituximab or abatacept, although data from an observational study of small cohorts suggest some risk of infections in its use after rituximab. Thus, more information will have to be obtained from further trials or soon become available from registries. Data from registries of patients receiving TCZ are currently limited,[65] but the registries will provide additional information on the use of co-medications or patients treated in the presence of comorbidities that were excluded from clinical trials, as patients in clinical practice are usually more heterogeneous in these respects compared with trial populations.

Screening before initiating TCZ

In general, patients should be well informed about the risks and benefits of TCZ therapy (level 5, grade D).

Initiation of TCZ should be preceded by obtaining a detailed history regarding chronic or recent co-morbidity, such as cardiovascular, liver and pulmonary diseases, recurrent infections, allergies, gastrointestinal perforations or diverticulitis, pregnancy or plans to become pregnant, and a complete physical examination to consider possible contraindications in all patients, especially the elderly. Special attention should be paid to vaccinations which should be performed in accordance with respective recommendations ideally before the administration of TCZ.[66] During TCZ therapy vaccination with live vaccines (which includes rubella and shingles vaccines) should be avoided (level 5, grade D).

A history of diverticulitis (note, not diverticulosis) should alert the patient and treating physician, to a heightened risk of gastrointestinal perforations during TCZ therapy. Gastrointestinel (GI) perforations have been reported (incidence 0.1–0.2%), especially in patients with such history[35 55 67] (level 4, grade C), although most were on glucocorticoids or non-steroidal antirheumatic drugs (NSAIDs). Indeed, recent data indicate that RA patients, regardless of DMARD therapy, have a generally increased rate of GI perforation including both the upper and lower GI tract, and the risk factors for this complication are glucocorticoid therapy, NSAIDs, and diverticulitis history among others.[68] At this time, further information is needed to understand whether TCZ or other IL-6 inhibitors further increase the risk of this complication beyond that observed in the general RA population. Until then, however, when IL-6 blocking therapy is prescribed in such patients, efforts to eliminate or mitigate known risk factors for perforation should be undertaken where possible, and vigilance for this potential complication should be maintained.

In clinical trials of TCZ, patients with RA were screened for hepatitis B and C and excluded if testing positive. Likewise, patients were excluded if they had active liver disease, indicated by screening and baseline concentrations of alanine or aspartate aminotransferase of 1.5 times the upper limit of normal (ULN) or more. Of note, hepatic transaminase increases occurred more frequently when TCZ was used in combination with MTX as compared to monotherapy. The safety of TCZ in patients with active hepatitis B or C virus (HBV, HCV) infections is currently unknown. Clearly, in the presence of acute viral hepatitis TCZ therapy is contraindicated. Also, in patients with chronic hepatitis B with poor liver function, TCZ therapy is not recommended. In Japan, several case reports have been published in which two HBV patients, in the context of concomitant antiviral therapy, and one HCV patient were successfully treated with TCZ,[69–72] and in a postmarketing surveillance report no hepatobiliary disorders due to reactivation of hepatitis B or C have been seen[73] (level 4, grade C). Thus, in patients with chronic hepatitis B and moderate to good liver function, treatment with antiviral agents should be performed before considering TCZ therapy. In HBV carriers or in patients with latent HBV infection (ie, HBs antigen negative, HBc or HBs antibody positive) who show positive HBV DNA in peripheral blood, prophylaxis should be considered before starting TCZ. Thus, until further safety data are collected, TCZ treatment in patients with chronic viral hepatitis can currently not be recommended without antiviral prophylaxis in case of hepatitis B,[71] especially since reactivation of viral hepatitis has been reported for other biological agents, such as TNF-inhibitors, abatacept and rituximab[74–77] (level 5, grade D).

While preclinical studies have not clearly defined the role of IL-6 in the defence against *Mycobacterium tuberculosis*,[78] the occurrence of tuberculosis has been reported in clinical trials and postmarketing surveillance studies of TCZ[73 79] (level 4, grade C) and, therefore, patients should be screened for latent tuberculosis according to local recommendations in the same manner as for other biologicals; in the pivotal clinical trials patients had been screened for tuberculosis. Chemoprophylaxis prior to TCZ initiation should be given in patients diagnosed with latent tuberculosis infection (level 5, grade D). Patients with active tuberculosis are contraindicated for treatment with TCZ.

Glucocorticoid therapy should be recorded and minimised or tapered as rapidly as possible, since there are indications that the risk of serious infections including opportunistic infections is higher in TCZ treated patients with concomitant glucocorticoid therapy than in those without[73] (level 4, grade C).

Regarding safety during and after pregnancy, currently only limited data exist;[80 81] there is no apparent evidence that IL-6 plays a role in fertility or gestation or TCZ leads to malformations, though IgG antibody transmission across the placenta has been demonstrated with other biological agents. Nevertheless, women of childbearing potential should use effective contraception during and until 3 months after cessation of therapy. Currently it cannot be suggested to continue TCZ therapy in women who become pregnant because only insufficient safety data exist; on the other hand, therapeutic abortion relies on a thorough discussion between the physician and the mother. Also, breast-feeding should not be done during TCZ therapy (level 5, grade D).

Administration of TCZ in combination therapy and monotherapy

TCZ is administered as a monthly intravenous infusion, usually over 1 hour. The approved initial dose in Europe and most other regions of the world is 8 mg/kg, while in the USA it is 4 mg/kg. The maximum recommended dose is 800 mg for people with ≥100 kg bodyweight.[35 55] A subcutaneous formula is currently under investigation. Other IL-6 blockers that are currently in phase 2 or 3 studies (see table 1A) are also applied by the subcutaneous route.

TCZ is approved for use in combination with MTX and as monotherapy if MTX is not tolerated or inappropriate. However, TCZ has also been used in combination with a variety of other sDMARDs.[52 82]

While it is recommended to lower the dose of TCZ when certain adverse effects occur (see below), it is not clear at present how one should proceed once patients reach the treatment target, such as clinical remission or sustained low disease activity: can the dose be reduced, the interval between infusions expanded, or should full treatment be continued? In a Japanese study, only 13% of the patients maintained low disease activity over 1 year after cessation of TCZ without use of any