Northern highlights in rheumatology

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The Scandinavian Congress of Rheumatology has been held every other year since 1946 in one of the five Scandinavian countries: Sweden, Norway, Denmark, Iceland and Finland. These congresses focus on clinical and basic research in Scandinavian countries, with a strong history of research in epidemiology, diagnosis and treatment of rheumatic diseases.

The 32nd Scandinavian Congress of Rheumatology, named 'Northern High-Lights in Rheumatology', was held in Levi, Lapland. The meeting covered important clinical topics such as diagnostics, monitoring, imaging modalities and treatment strategies for rheumatic diseases. Work disability and its prevention, chronic widespread pain, updates of rheumatologic 'emergencies' and pediatric rheumatology were discussed. Topics in the basic science lessons included the role of T cells in chronic inflammation, lymphocyte tracking in arthritis and other autoimmune diseases, gene polymorphisms and the role of adipokines in inflammation and rheumatic diseases. More than 50 abstracts were selected for oral presentations. Some of the highlights of the congress are presented in this report.

Decreased low-back pain & osteoarthritis in the general population of Finland

Markku Heliövaara (National Public Health Institute, Helsinki, Finland) presented epidemiological research concerning trends in musculoskeletal health in Finland over the past three decades [1], based on the Mini-Finland Health Survey in 1978–1980 [2], and the Heal th 2000 Survey in 2000 [3]. Both studies included approximately 8000 individuals.

In the period 1978–1980, the age-adjusted prevalence of chronic low-back syndrome was 18% in men and 17% in women. In 2000–2001, this condition was diagnosed in 11% of both genders. The downward trend was even more marked in the prevalence of chronic neck pain syndrome, with a 50% reduction over the 20 years.

In the period 1978–1980, knee osteoarthritis was diagnosed in 6% of men and 15% of women, whereas in 2000–2001, the prevalence rates were 6 and 8%, respectively. The reduction among women occurred mainly in those aged under 75 years. No substantial change was observed in the prevalence of hip osteoarthritis or chronic shoulder syndrome.

An interview concerning symptoms was carried out in both surveys. No change in the age-adjusted prevalence of back, neck or knee complaints had occurred. However, a clear-cut cohort effect was observed: a reduction in the report of symptoms was seen in the younger population, whereas the complaints continued to increase in the older population.

These data suggest that musculoskeletal health in the Finnish population is improving [3]. This development may reduce the burden of aging on healthcare and social insurance. Reasons for the improvement remain unclear. Improvements have occurred in the known risk factors for musculoskeletal diseases, including the physical demands of work, the number of work-related accidents, and poor living conditions, resulting in better health in the younger age group. On the other hand, obesity in men has become increasingly common, which may explain why the prevalence of knee osteoarthritis is not decreasing in men, in contrast to women.

Heliövaara's plenary presentation concerning the trends in musculoskeletal health was of special interest as the data are unique; similar epidemiology research is uncommon in other countries.

Data from the FIN-RACo trial

Observations from the Finnish Rheumatoid Arthritis (RA) Combination Therapy Trial (FIN-RACo) [4] were presented by several investigators.

In the opening plenary session, Marjatta Leirisalo-Repo (Helsinki University Central Hospital, Helsinki, Finland) [5] reviewed results of clinical trials that defined the treatment goal as remission or low disease activity, including FIN-RACo [4], as well as Tight Control for Rheumatoid Arthritis (TICORA) [6], BeSt [7], and Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) [8]. Based on the results of these studies, she concluded that, to achieve the best outcome, the treatment should be targeted at remission. Factors contributing to good long-term outcomes include early institution of treatment and strict monitoring of the treatment response, with flexible dosing of, and switching between, drugs. Early suppression of inflammation is crucial to prevent radiographic destruction, work disability

and high costs of the disease to society. She concluded that induction of a cure in RA with new interventions may be a realistic possibility in the future.

Vappu Rantalaiho (Tampere University Hospital, Tampere, Finland) presented 11-year results of the FIN-RACo study [9]. FIN-RACo enrolled 195 patients with early RA in 18 rheumatology clinics in 1993–1995 [4]. The patients were randomized to two treatment arms for 2 years: 97 received a combination of methotrexate, sulfasalazine, hydroxychloroquine and prednisolone, while 98 received monotherapy with sulfasalazine (with or without prednisolone), in which methotrexate was later substituted in 51 patients. The treatment goal was remission and doses of DMARDs were required to be adjusted to reach this goal if possible. The primary outcome measure of the FIN-RACo study was a tight ACR remission, which was met by 37% of patients in the combination group and by 18% in the monotherapy group ($p = 0.003$) at 2 years [4], whereas the rate of remission was 68% in the combination group and 41% in the monotherapy group according to a Disease Activity Score (DAS28) remission of less than 2.6 [10].

The FIN-RACo patients were invited to continue in a longitudinal observational study after the 2-year study period [9]. At 11 years, 67 patients from the original combination group and 70 patients from the original monotherapy group were assessed. In these patients, the prevalence of minimal disease activity (MDA) at 2 years had been 70% in the combination group versus 50% in the monotherapy group. At 11 years, the prevalence of MDA was 74% in the combination group among those who had MDA at 2 years versus 51% in the monotherapy group among those who had MDA at 2 years ($p = 0.024$). Among patients with MDA not present at 2 years, a similar percentage of 34 and 35% had MDA at 11 years in the combination and monotherapy group, respectively. Therefore, it appears that once MDA is achieved at 2 years by a combination treatment, it can be sustained in three out of four patients over the long term (11 years).

Kari Puolakka (Lappeenranta Central Hospital, Lappeenranta, Finland) gave a plenary presentation of work disability studies in the FIN-RACo trial [11]. Work disability is a major problem in RA: until recently, 20–30% of patients with early RA became work disabled over 3 years and 50–60% over 10 years [12]. FIN-RACo patients in the initial combination group were more likely to maintain their capacity to continue paid work over 5 years compared with the monotherapy group [13]. Furthermore, 54% of patients who did not have ACR20 responses over 6 months became permanently work disabled over 5 years, compared with 22% of those who had ACR 20 or 50 responses. Most importantly, if inflammation was controlled to a status of remission at 6 months, no patient was receiving work disability payments at 5 years [14,15]. This observation indicates that improvement rates of ACR20 or 50% are suboptimal goals of therapies for patients with early RA.

Can traditional DMARDs or prednisone be withdrawn?

Tarja Tiippana-Kinnunen (Helsinki University Central Hospital, Helsinki, Finland) presented an evaluation of the influence of DMARD withdrawal on 15-year outcomes in a cohort of patients with early RA [16]. A cohort of 87 DMARD-naive RA patients (disease duration ≤1 year) was enrolled in an observational study between 1986 and 1989 in the Helsinki area. A DMARD was initiated in all patients according to a saw-tooth strategy [17]. DAS28 (0–10), Larsen radiographic score (0–200) and the Health Assessment Questionnaire (0–3) were measured to assess outcomes at 15 years.

During 15 years, ten patients had died, six dropped out of follow-up, and diagnosis had changed in one patient. Thus, data from 70 patients were analyzed for the 15-year follow-up study. Patients were classified into three groups: 50 patients continued DMARDs throughout the follow-up (group I); nine patients discontinued and restarted a DMARD owing to a flare (group II); and 11 patients discontinued DMARDs permanently (group III).

At 15 years, the mean DAS28 was highest in group II (3.68) compared with 3.36 in group I and 2.08 in group III ($p = 0.0018$). Radiographic progression was most extended in group I (mean Larsen: 54), compared with 25 in group II and 12 in group III ($p < 0.001$). Functional capacity (mean Health Assessment Questionnaire) remained good in all groups: 0.60 in group I, 0.38 in group II and 0.24 in group III ($p = 0.049$).

In this cohort, DMARDs were discontinued in 29% of patients with low disease activity or remission. However, disease flared in approximately half of these patients. Therefore, careful follow-up is needed to respond rapidly to possible flares if a DMARD is discontinued.

Theodore Pincus (New York University Hospital for Joint Diseases, New York, NY, USA) reported a randomized, controlled, double-blind withdrawal trial [18] in patients with RA who were treated in standard clinical care with low-dose prednisone of 1–4 mg/day added to DMARDs. The protocol included three phases:

- 'Equivalence' – each patient took 1 mg study prednisone tablets instead of the usual 1 mg prednisone for 3 months, to ascertain efficacy prior to randomization;
- 'Transfer' – patients who reported equivalence were randomized to either 1 mg prednisone or identical placebo tablets, and transferred at 1 mg per month over 1–5 months, according to baseline stable dosage;
- 'Comparison' – patients were maintained over 6 months after 'transfer' with either prednisone or placebo.

The primary outcome was withdrawal due to lack of efficacy.

In total, 31 patients were randomized into this clinical trial, 28 of whom completed the trial or withdrew owing to lack of efficacy. A total of ten out of 13 patients who were randomized to prednisone completed the study, compared with four out of 15 patients who

were randomized to placebo, while three prednisone patients and 11 placebo patients withdrew for lack of efficacy ($p = 0.02$). No meaningful adverse events were reported, as anticipated, as all patients had taken stable doses of 1–4 mg of prednisone prior to the study.

The efficacy of a low dose (1–4 mg) of prednisone was documented in this clinical trial; the finding of statistically significant differences in only 28 patients may suggest a robust treatment effect.

Adipokines

Adipokines are members of a family of small bioactive molecules/peptides, originally described as products of adipose tissue regulating carbohydrate metabolism. It has recently been recognized that these molecules are produced by leukocytes, and they have since emerged as novel mediators of inflammatory processes and innate immune responses. Studies on the role of leptin, visfatin, adiponectin and resistin in the development of autoimmune conditions were presented and discussed at the congress.

Eeva Moilanen (University of Tampere, Tampere, Finland) [19] reported studies concerning the proinflammatory role of leptin, alone or in combination with IL-1, on cartilage explants from knee joints of patients with osteoarthritis. Exposure of these cartilage explants to recombinant leptin was associated with the release of proinflammatory cytokines and inducible nitric oxide synthase (iNOS). Interestingly, the leptin-induced expression of proinflammatory cytokines was dependent on the presence of nitric oxide, and could not be found in cartilage explants treated with a selective iNOS-inhibitor. The intracellular signaling pathways activated by leptin and required for cytokine expression and inflammatory effects were found to be mediated by Jun N-terminal kinase and p38 mitogen-activated kinases, as well as the transcription factor NF-κB.

Linda Nilsson Möllers [20] (University of Göteborg, Göteborg, Sweden) reported a study on interference between different adipokines, using the intra-articular expression pattern of visfatin and adiponectin as a working model. Visfatin and adiponectin levels in paired samples of blood and synovial fluid from 64 patients with RA were compared with samples from 33 healthy controls and 19 individuals with knee trauma. It was shown that visfatin and adiponectin had different expression patterns inside the inflamed RA joints. Visfatin levels were significantly increased intra-articularly compared with circulating levels in the same patient. Vistafin levels were also significantly correlated to the intensity of inflammation in patients with RA, reflected in leukocyte counts in synovial fluid and levels of C-reactive protein. By contrast, adiponectin levels were significantly decreased in synovial fluid compared with blood, suggesting local consumption of adiponectin in intra-articular inflammation. Furthermore, stimulation of human leukocytes with visfatin showed an inhibitory effect on the expression of leptin, resistin and adiponectine, while stimulation with adiponectin did not affect expression of other adipokines.

Elisabeth Almer (University of Göteborg) [21] reported a role for resistin as a novel marker of inflammation in patients with primary Sjögren's syndrome. Resistin levels in saliva were directly related to the inflammation scores of biopsies of minor salivary glands and to acute-phase reactants in the circulation. A strong correlation was observed between secreted resistin levels and the intensity of leukocyte infiltration of the glands. An attempt to alleviate resistin levels in patients with Sjögren's syndrome *in vivo* using dehydroepiandrosterone was ineffective, suggesting the importance of local, rather than systemic, mechanisms in regulating resistin levels in saliva. Resistin has previously been shown to be a pro-inflammatory cytokine able to induce local inflammation intra-articularly, with accumulation in the synovial fluid of patients with RA [22]. This study indicates that resistin is an important local mediator of inflammation in human salivary glands.

Human resistin has been previously reported to upregulate inflammatory responses by modulating expression of proinflammatory cytokines in human leukocytes [22]. Maria Bokarewa from Anrej Tarkowski's research group (University of Göteborg) presented results of the structural requirements for resistin interaction with the surface of leukocytes. It was shown that Toll-like receptor (TLR)-4 is a surface protein that mediates the proinflammatory properties of resistin. Different approaches, including the introduction of neutralizing antibodies targeting TLR-4 and resistin, respectively, immunoprecipitation, short inhibitory RNA and experiments with genetically modified cells, indicate a specific interaction between resistin and TLR-4 followed by MyD88 and NF-κB activation. These data indicate that resistin is an endogenous ligand of TLR-4.

Sports & keeping fit: useful for patients with RA?

Traditionally, patients with RA were advised to avoid or limit physical exercise for fear that physical exercise might increase disease activity and harm joints. Patients with early RA have been shown to have lower muscle strength compared with control subjects already at the time of diagnosis, indicating a lack of physical activity during early phases of the disease [23].

Arja Häkkinen (Jyväskylä Central Hospital, Jyväskylä, Finland) has questioned the traditional advice of caution concerning physical exercise and sports for patients with rheumatic diseases. One of her studies demonstrated that a 2-year intensive strength and aerobic training regime in early RA does not increase joint damage over 5 years [24,25]. Females with established RA are able to increase their muscle strength similarly to healthy control levels with intensive strength training over 21 weeks, with no detrimental effect on disease activity [26].

Together with Kaisa Mannerkorpi (University of Göteborg), Häkkinen gave a hands-on workshop to rheumatologists in the utilization of gym training, rubber bands and gym balls in a before-daylight workshop [27]. They emphasized that the general principles of strength training can be applied in patients with

arthritis. Strength training with high loads, using slow movement/action velocities, primarily improves maximal force and muscle mass. Explosive force production is trained with higher movement velocity, while muscular endurance is improved using low loads with a high number of repetitions. Progressive increase in the overall amount of training volume (number of sets, repetitions) will ensure the development. One repetition maximum method can be used to find proper load.

Over the past decade, the importance of exercise as a component of the management of RA has been recognized, with recommendations of regular physical exercise [28]. Reminders of these recommendations are needed as, in many countries, a low proportion of patients with RA exercise [29]. In patients with RA, physical training improves muscle force, aerobic capacity, balance and musculoskeletal functioning, and generates an improved sense of well-being, while decreasing inflammation and pain [24,30,31]. It is possible that regular physical exercise may have beneficial effects concerning cardiovascular morbidity and mortality in patients with RA, although existing evidence does not allow an estimate of the relative impact of physical inactivity on cardiovascular disease in RA [32]. Muscle-strength training and keeping fit might also postpone work disability in some RA patients [33].

Rheumatoid arthritis registers

Scandinavia is the promised land of population registers [34]. Registers date back to the sixteenth century in the former Sweden–Finland. Genealogic information has been collected by Icelanders through the nation's history for 11 centuries.

All Scandinavian countries have established registers of patients who receive biologic and traditional treatments for rheumatic diseases. Observations from these databases were presented in many sessions in the conference.

The safety of biologic agents can be reliably studied only in large databases. Lars Klareskog (Karolinska University Hospital, Stockholm, Sweden) presented an analysis of the Swedish biologic register showing an increased risk of lung cancer and lymphoma in patients who were treated with abatacept when compared with general population figures [35]. However, the risk was at the same level as that of patients with RA who were not treated with biologic agents. In fact, Scandinavian population and cancer register data have been utilized since the 1960s, with observations of increased risk of lymphoma, leukemia, myeloma and lung cancer [36–40], but decreased risk of colorectal cancer [41,42] in patients with RA compared with the general population.

It remains unclear whether switching from one biologic treatment to another provides a lower, equal or better response compared with the first. Ronald van Vollenhoven (Karolinska University Hospital) presented data for the Swedish Stockholm Biologic Registry (STURE) concerning patients who had switched from one biologic therapy to another [43]. A switch occurred in 41% of patients who had started infliximab, in 22% of patients who had started etanercept and in 26% of patients who had started adalimumab. In patients who switched from infliximab to etanercept (n = 178) or from etanercept to infliximab (n = 25), the lowest DAS28 was significantly better during the second biologic treatment period. In patients who switched from infliximab to adalimumab (n = 72), from etanercept to adalimumab (n = 24) or from adalimumab to etanercept, no statistically significant differences were seen in the lowest DAS28 between the first and the second agent. These results suggest that the switch from etanercept to infliximab or from infliximab to etanercept might provide additional therapeutic benefits in many patients.

Conclusion

The Northern Highlights of Rheumatology was enjoyed by almost 400 participants from Scandinavia and from 20 other countries under the Aurora Borealis in snowy Levi.

The value of small rheumatology meetings may be questioned in view of large, professionally conducted global annual meetings of the ACR and the EULAR, with excellent opportunities for learning and socializing. However, smaller meetings provide opportunities for interactions among people from nearby geographical areas, for presentations from younger individuals in the early stages of career development, and an ambience not available at large meetings. Attendees at the 32nd Scandinavian Congress found numerous opportunities to increase their knowledge of rheumatology and meet new colleagues.

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Bibliography

1. Heliövaara M: Health in Finland according to national surveys in 1975–2000. *Scand. J. Rheumatol.* 37(Suppl. 123), 5 (2008).
2. Heliövaara M, Aho K, Knekt P, Aromaa A, Maatela J, Reunanen A: Rheumatoid factor, chronic arthritis and mortality. *Ann. Rheum. Dis.* 54, 811–814 (1995).
3. Riihimaki H, Heliövaara M, Heistaro S *et al.*: Musculoskeletal diseases. In: *Health and Functional Capacity in Finland. Baseline Results of the Health 2000 Health Examination Survey.* Aromaa A, Koskinen S (Eds). National Public Health Institute, Helsinki, Finland, 47–50 (2002).
4. Möttönen T, Hannonen P, Leirisalo-Repo M *et al.*: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 353, 1568–1573 (1999).

5. Leirisalo-Repo M: Traditional DMARDs and/or biological agents in RA – what have we learned? *Scand. J. Rheumatol.* 37(Suppl. 123), 5 (2008).
6. Grigor C, Capell H, Stirling A *et al.*: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364, 263–269 (2004).
7. Allaart C, Breedveld F, Dijkmans B: Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. *J. Rheumatol.* 80, 25–33 (2007).
8. Verstappen S, Jacobs J, van der Veen M *et al.*: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann. Rheum. Dis.* 66(11), 1443–1449 (2007).
9. Rantalaiho V, Kautiainen H, Jarvenpaa S *et al.*: Sustained minimal disease activity with initial combination treatment in early rheumatoid arthritis. The 11-year results of the FIN-RACo study. *Scand. J. Rheumatol.* 37(Suppl. 123), 37 (2008).
10. Makinen H, Kautiainen H, Hannonen P *et al.*: Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J. Rheumatol.* 34(2), 316–321 (2007).
11. Puolakka K: Work disability in rheumatoid arthritis. *Scand. J. Rheumatol.* 37(Suppl. 123), 5 (2008).
12. Sokka T: Work disability in early rheumatoid arthritis. *Clin. Exp. Rheumatol.* 21, S71–S74 (2003).
13. Puolakka K, Kautiainen H, Mottonen T *et al.*: Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis. A five-year randomized followup trial. *Arthritis Rheum.* 50, 55–62 (2004).
14. Puolakka K, Kautiainen H, Mottonen T *et al.*: Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. *Ann. Rheum. Dis.* 64, 130–133 (2005).
15. Puolakka K, Kautiainen H, Mottonen T *et al.*: Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum.* 52(1), 36–41 (2005).
16. Tiippana-Kinnunen T, Paimela L, Kautiainen H, Leirisalo-Repo M: 15-year outcome in a cohort of early rheumatoid arthritis; analysis of a subgroup of patients with DMARD withdrawal. *Scand. J. Rheumatol.* 37(Suppl. 123), 27 (2008).
17. Fries JF: Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. *J. Rheumatol.* 17(Suppl. 22), 12–15 (1990).
18. Pincus T, Swearingen C: Efficacy of low dose prednisone (1–4mg/day) in patients with RA: a randomized placebo controlled double-blind withdrawal trial. *Scand. J. Rheumatol.* 37(Suppl. 123), 28 (2008).
19. Koskinen A, Vuolteenaho K, Kukkonen M, Nieminen R, Moilanen T, Moilanen E: Leptin induces IL-6 and IL-8 production in human OA cartilage in a NO-dependent manner. *Scand. J. Rheumatol.* 37(Suppl. 123), 30 (2008).
20. Nilsson Möllers L, Nagaev I, Shestakov A, Smith U, Tarkowski A, Bokarewa M: Different regulation of visfatin and adiponectin in rheumatoid arthritis. *Scand. J. Rheumatol.* 37(Suppl. 123), 30 (2008).
21. Almer E, Forsblad d'Elia H *et al.*: Salivary resistin reflects inflammation in Sjögren Syndrome. *Scand. J. Rheumatol.* 37(Suppl. 123), 30 (2008).
22. Bokarewa M, Nagaev I, Dahlberg I, Smith U, Tarkowski A: Resistin, an adipokine with potent proinflammatory properties. *J. Immunol.* 174(9), 5789–5795 (2005).
23. Häkkinen A, Sokka T, Kotaniemi A *et al.*: Muscle strength characteristics and central bone mineral density in women with recent onset rheumatoid arthritis compared with healthy controls. *Scand. J. Rheumatol.* 28, 145–151 (1999).
24. Häkkinen A, Sokka T, Kotaniemi A, Hannonen P: A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum.* 44, 515–522 (2001).
25. Häkkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P: Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up. *Ann. Rheum. Dis.* 63, 910–916 (2004).
26. Häkkinen A, Pakarinen A, Hannonen P *et al.*: Effects of prolonged combined strength and endurance training on physical fitness, body composition and serum hormones in women with rheumatoid arthritis and in healthy controls. *Clin. Exp. Rheumatol.* 23(4), 505–512 (2005).
27. Häkkinen A, Mannerkorpi K: Sports and keeping fit – is it for patients with RA? *Scand. J. Rheumatol.* 37(Suppl. 123), 23 (2008).
28. Work Group Recommendations: 2002 Exercise and Physical Activity Conference, St: Louis, Missouri. Session V: evidence of benefit of exercise and physical activity in arthritis. *Arthritis Rheum.* 49(3), 453–454 (2003).
29. Sokka T, Häkkinen A, Kautiainen H *et al.*: Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum.* 59(1), 42–50 (2008).
30. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines of the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum.* 46(2), 328–346 (2002).
31. Stenstrom CH: Therapeutic exercise in rheumatoid arthritis. *Arthritis Care Res.* 7(4), 190–197 (1994).
32. Turesson C, Matteson EL: Cardiovascular risk factors, fitness and physical activity in rheumatic diseases. *Curr. Opin. Rheumatol.* 19(2), 190–196 (2007).
33. Häkkinen A: Active exercise in the prevention of work disability in rheumatic diseases. *Scand. J. Rheumatol.* 37(Suppl. 123), 9 (2008).
34. Sokka T: National databases and rheumatology research I: longitudinal databases in Scandinavia. *Rheum. Dis. Clin. North Am.* 30(4), 851–867 (2004).
35. Simon T, Smitten A, Meng M *et al.*: Observed and expected malignancies in the rheumatoid arthritis abatacept clinical development program: an updated epidemiological assessment. *Scand. J. Rheumatol.* 37(Suppl. 123), 26 (2008).
36. Isomäki HA, Hakulinen T, Joutsenlahti U: Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J. Chronic Dis.* 31, 691–696 (1978).
37. Hakulinen T, Isomäki H, Knekt P: Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. *Am. J. Med.* 78(Suppl. 1A), 29–32 (1985).
38. Kauppi M, Pukkala E, Isomaki H: Excess risk of lung cancer in patients with rheumatoid arthritis. *J. Rheumatol.* 23(8), 1484–1485 (1996).
39. Gridley G, McLaughlin JK, Ekbom A *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J. Natl Cancer Inst.* 85(4), 307–311 (1993).

40. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L: Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case–control study. *BMJ* 317(7152), 180–181 (1998).
41. Kauppi M, Pukkala E, Isomaki H: Low incidence of colorectal cancer in patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 14(5), 551–553 (1996).
42. Gridley G, McLaughlin JK, Ekbom A *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J. Natl Cancer Inst.* 85(4), 307–311 (1993).
43. van Vollenhoven R, Joelsson J, Cullinane Carli C, Klareskog L: Switching between anti-TNFs: a comparison of maximum efficacy with each tretment – data from the STURE registry. *Scand. J. Rheumatol.* 37(Suppl. 123), 26 (2008).

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