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Notes

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ABSTRACT

Objective: To determine the effect of changing from etanercept or methotrexate monotherapy to etanercept plus methotrexate combination therapy on radiographic progression in rheumatoid arthritis (RA) patients.

Methods: Patients enrolled in this 1-year open-label study previously completed a 3-year blinded study in which they received methotrexate or etanercept monotherapy or the combination of both. All patients received the combination of etanercept 25 mg subcutaneously twice weekly plus oral methotrexate up to 20 mg/week. The primary radiographic endpoint was a change in modified total Sharp score (TSS), as assessed by blinded readers.

Results: At baseline, patients previously receiving methotrexate monotherapy (etanercept-added, n = 52) or etanercept monotherapy (methotrexate-added, n = 68) had moderate disease activity levels (mean disease activity score (DAS) of 2.6 and 2.5, respectively), whereas patients previously receiving combination therapy (n = 90) had a low disease activity level (mean DAS of 2.0). The addition of etanercept to methotrexate monotherapy resulted in a significant reduction in radiographic progression (p<0.05). Mean TSS changes in the previous year versus the current year were +1.79 versus +0.25 for the etanercept-added group (p<0.05); +0.51 versus −0.18 for the methotrexate-added group (NS) and +0.42 versus +0.24 for the combination group (NS).

Conclusion: In these RA patients with on average moderate disease activity despite previous methotrexate monotherapy, combination treatment with etanercept and methotrexate inhibited radiographic progression and improved radiographic outcomes. These data, in conjunction with the previously published clinical data, support the use of combination therapy in RA patients with moderate disease activity.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease, which occurs in approximately 1% of the adult population in western countries,[1 2] and is associated with progressive joint destruction, functional disability and increased mortality.[3–8] Several studies have shown a rapid rate of progression in erosion and cartilage destruction in the early years of the disease that appeared to decrease in later disease.[7 9–13] In a 3-year study in patients with early RA, van der Heijde et al[10] observed an initial rate of radiographic progression of 14 standard units (SU) in total Sharp score (TSS), out of a maximum of 448 SU, in the first year and a progression to 9 SU in the subsequent 2 years during treatment with conventional disease-modifying antirheumatic drugs (DMARD). Moderate loss of functional ability may develop in half of affected individuals within 2 years of RA diagnosis.[8] Therefore, treatment of RA with effective therapy early in the disease course is recommended, with the goal of long-term remission and prevention or limitation of joint damage and functional loss.[14]

Among the DMARD currently used in RA, methotrexate is often selected first, particularly for patients with more active disease, because randomised, controlled clinical trials have established its efficacy in improving symptoms and function and in slowing the progression of joint erosion.[14] However, several trials have shown that joint destruction continues even with the use of high-dose methotrexate[15–20] as well as sequential DMARD monotherapy or step-up combination DMARD therapy.[21] In addition, the majority of patients discontinue most conventional DMARD regimens within 2 years, most often because of insufficient efficacy or intolerability.[22] Biological drugs that selectively block tumour necrosis factor (TNF), a pro-inflammatory cytokine involved in the pathogenesis of RA,[23] have become an important therapeutic option in RA. Clinical trial data have demonstrated that the use of TNF antagonists, alone or in combination with methotrexate, is effective in improving both clinical and radiographic outcomes in patients with RA.[16–20 24–28] Although these newer antirheumatic medications and regimens are highly effective, there is still more to learn about which patients should be treated with these therapies.

In this study, we provide the radiographic results of a 1-year study in which patients with RA who previously completed 3 years of a blinded therapy with methotrexate or etanercept alone or a combination of both all received treatment with the combination of etanercept and methotrexate for 1 year. The results of the clinical outcomes[25] demonstrated that patients with partial response to long-term monotherapy and a mean moderate disease activity level can obtain a greater benefit with combination therapy and that patients can

sustain the benefit or continue to show improvement through 4 years of combination therapy.

PATIENTS AND METHODS

A detailed description of the study design is provided elsewhere.[25] In brief, RA patients who completed 3 years of treatment with methotrexate, etanercept, or a combination of both in a double-blind study[18 29 30] were eligible to enroll in the current study. All enrolled patients received both open-label etanercept 25 mg subcutaneously twice weekly and oral methotrexate at individualised doses up to 20 mg/week. Radiographic evaluations were performed at baseline of the current study and at year 1.

The study protocol and an informed consent form received approval by the independent ethics committee or institutional review board at each institution before study initiation. All participating patients provided written informed consent before enrollment in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Radiographic assessments

Radiographs of the hands, wrists and forefeet were taken at the baseline visit (post 3-year, double-blinded portion of the study) and at week 52 or the final study visit. In addition, the films from years 2 and 3 of the prior double-blind study were re-analysed, allowing evaluation of changes in radiographic progression before and after the initiation of combination therapy in patients receiving previous monotherapy and with the continuation of combination therapy in those receiving previous combination therapy. The primary radiographic endpoint was the change from baseline in the van der Heijde-modified TSS,[31] which was calculated from baseline to year 1 or the final study visit for all patients with valid radiographic data. Other radiographic assessments included changes from baseline

to year 1 in erosion and joint space narrowing (JSN) scores; differences in annualised rates of change in modified TSS, along with erosion and JSN scores, from the year before the current study (when patients were receiving blinded monotherapy or combination therapy) and the current 1-year study period; and the proportion of patients with radiographic non-progression, defined as modified TSS change of 0.5 or less and as modified TSS change of 0.0 or less. The changes from baseline in modified TSS were presented in cumulative probability plots to allow visualisation of all radiographic data over the 1-year period. Frequency distributions of the observed cumulative proportion, by which scores were ranked from lowest to highest by treatment group and expressed as a cumulative percentage of all scores, were plotted against the actual change in modified TSS.

Radiographs from each patient were acquired according to procedures prepared by Bio-Imaging Technologies (Newtown, Pennsylvania, USA), which also digitised and archived the images. Two independent physicians read the digitised image sets of radiographic films for each patient in random sequence using a computer-assisted masked reading method. The readers remained blinded to the treatment groups of the previous 3-year study and to the order of radiographs throughout the reading process. An image set was composed of images from three time points: the final visits of year 2 of the previous double-blind study and the baseline visit (same as year 3 of the previous study) and the final visit of the current study. The average score of the two readers was used in the analyses. To validate reader reliability, inter-reader and intra-reader variability intra-class correlations were calculated. Five per cent of images were read twice and scores from the second reading were compared with those from the first reading to determine intra-reader correlations. Status scores on all images from all patients read by both readers were used to calculate inter-reader variability.

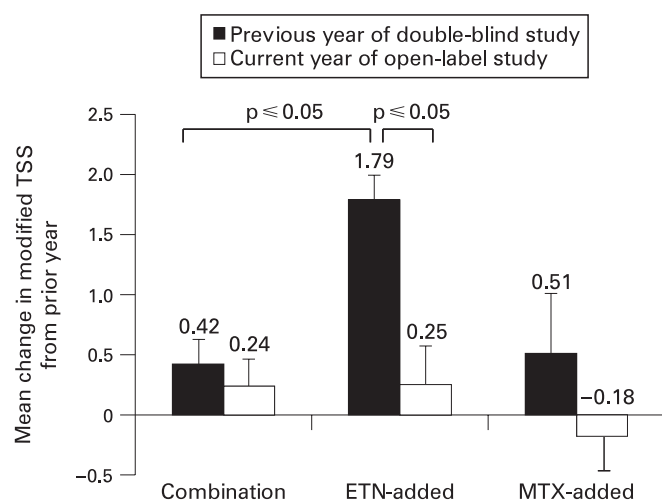**Figure 1** Patient disposition. ETN, etanercept; MTX, methotrexate.
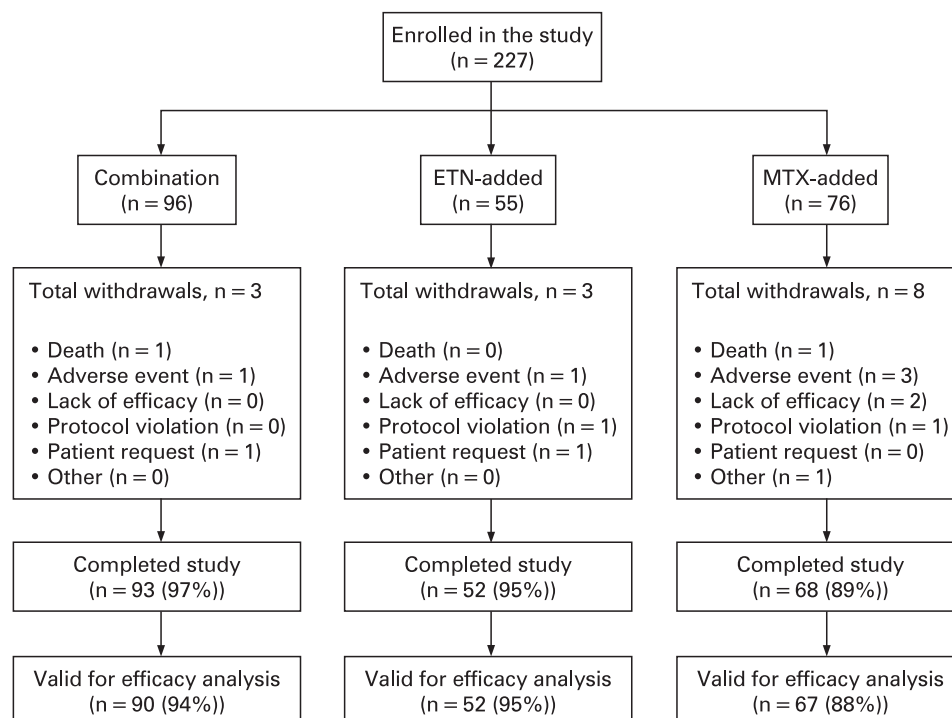
Figure 2 Mean change in modified total Sharp score (TSS) by treatment group from year 2 to year 3 of the previous double-blind study and from baseline to year 1 of the current study. ETN, etanercept; MTX, methotrexate.

Statistical analysis

The number of patients who completed year 3 of the previous double-blind study (n = 327) determined the sample size in this study, because only these patients were eligible for enrollment in the current open-label extension. Changes from baseline in modified TSS and erosion and JSN scores were analysed in all enrolled patients who received at least one dose of study drug and had readable baseline and on-therapy radiographs for the current 1-year study. For patients who did not complete the study, radiographs were taken at the final study visit and radiographic progression was imputed by linear extrapolation.

Radiographic assessments were analysed using an analysis of covariance (ANCOVA) model based on the ranks of the average scores from the two readers, including factors for baseline modified TSS rank, treatment group and methotrexate use before the original double-blind study initiation as covariates. ANCOVA results were accompanied by 95% CI. Radiographic non-progression (modified TSS change $\leqslant 0.5$ and modified TSS change $\leqslant 0.0$) was analysed using a Mantel–Haenszel approach, with stratification by study centre and prior methotrexate use. Inter-reader and intra-reader correlation coefficients were determined by analysis of variance.[32]

Clinical efficacy and safety analyses were performed using a modified intention-to-treat approach in which all patients who were randomly assigned and received at least one dose of study drug were included. The last-observation-carried-forward method was used to account for missing data when assessing clinical endpoints. All tests and confidence intervals were two-sided at an alpha of 0.05.

RESULTS

Patients and disposition

Of 686 patients randomly assigned in the original double-blind study,[29] 327 completed all 3 years of treatment. One hundred of these patients did not participate in the current study because they elected not to continue (n = 19) or their site discontinued participation in the study for non-medical reasons (n = 81), the most common being investigator lack of interest and regulatory document submission delays.

Of the 246 patients eligible to participate in this study, 227 patients (92.3%) were enrolled: 96 patients were previously treated with the combination of etanercept and methotrexate (combination); 55 patients with methotrexate monotherapy (etanercept-added); and 76 patients with etanercept monotherapy (methotrexate-added). Seventeen of the 227 enrolled patients (7.5%) were excluded from the radiographic intention-to-treat population (six patients in the combination group, three patients in the etanercept-added group and eight patients in the methotrexate-added group) because the required radiographs were not obtained (n = 10) or were unreadable (n = 7). An additional patient, who received etanercept monotherapy in the double-blind study, was excluded from the comparative analyses of radiographic progression between baseline (year 3 of double-blind treatment) and 1 year of open-label treatment because valid radiographs were not available from the original study. A total of 213 patients (93.8%) completed the 1-year study (fig 1); 209 patients were included in the radiographic intent-to-treat analysis.

Baseline demographics of the population enrolled in the current study were similar across treatment groups. Details have been published previously.[18 25 29 30] At baseline of this study, patients in the combination group had lower disease activity than those in the other two treatment groups. The mean disease activity score (DAS) of 2.0 in the combination group was in the low disease activity range (DAS <2.4) and significantly lower (p<0.05) than the mean DAS of 2.6 and 2.5 in the etanercept-added and methotrexate-added groups, respectively, which were both in the moderate disease activity range.

Radiographic efficacy

Changes in modified TSS and erosion and JSN scores

For all three treatment groups, the change in modified TSS was less during the current study on combination therapy than during the last year in the blinded study. However, only the addition of etanercept to methotrexate monotherapy resulted in a statistically significant reduction in radiographic progression during the year of open-label treatment (+1.79 to +0.25, p<0.05; fig 2). During treatment with combination etanercept and methotrexate therapy, all three groups demonstrated a mean radiographic progression of 0.25 or less. The mean changes in erosion scores during the last year of the double-blind study were +0.19, +0.66 and +0.21 for the combination, etanercept-added, and methotrexate-added groups, respectively. One year after combination therapy was administered to all patients in the current study, the erosion scores decreased to +0.06, +0.27 and 0.00, respectively. Similarly for JSN, the scores for the last year were +0.24, +1.12, +0.30 for the combination, etanercept-added, and methotrexate-added groups, respectively, which improved to +0.18, −0.02, −0.18 after treatment with combination therapy for 1 year.

Cumulative probabilities of individual changes from baseline in modified TSS during the 1-year period of the study, during which all patients received combination therapy with etanercept and methotrexate, are shown in fig 3. The majority of patients in all groups showed no progression or negative scores. The etanercept-added group included the highest percentage of patients with progression.

Radiographic non-progression

The percentage of patients with no progression of joint damage, when defined as modified TSS change of 0.5 or less, increased
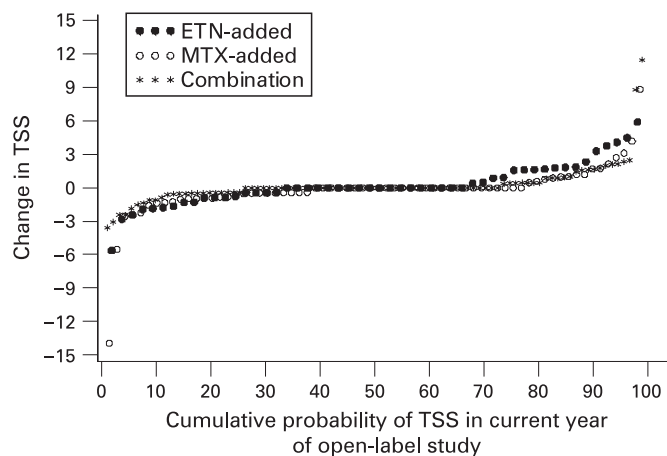
Figure 3 Probability plots of individual changes from baseline in modified total Sharp score (TSS) during the current 1-year study for the combination, etanercept (ETN)-added and methotrexate (MTX)-added groups.

Figure 4 Percentage of patients by treatment group with no radiographic progression, defined as change in modified total Sharp score (TSS) $\leqslant 0.5$, from year 2 to year 3 of the previous double-blind study and from baseline to year 1 of the current study. ETN, etanercept; MTX, methotrexate.

significantly for the etanercept-added group from year 3 to the current study (from 51.9% to 69.2%, p<0.05; fig 4); the other groups also demonstrated higher rates of non-progression in the study, but these were not significant. The results were similar when the radiographic non-progression definition was based on a modified TSS change of 0.0 or less. The etanercept-added group improved from 44.2% to 67.3% (p<0.05); the methotrexate-added group improved from 62.7% to 77.9% (p = NS) and the combination group improved from 68.9% to 73.3% (p = NS).

Inter and intra-reader correlation

Inter-reader correlation coefficients on erosion, JSN and TSS status scores at year 2 and year 3 ranged from 0.79 to 0.93; corresponding intra-reader correlation coefficients on radiological scoring data were 0.94 to 0.98.

DISCUSSION

The purpose of the current study was to determine whether previous monotherapy responders with a residual moderate disease activity level on average after long-term methotrexate or etanercept monotherapy would achieve further clinical and radiographic benefit from combination therapy with these agents. As reported elsewhere,[25] the combination group had low disease activity at the baseline of this study, whereas the etanercept-added and methotrexate-added groups had moderate disease activity. At week 52, all three treatment groups showed low disease activity (DAS <2.4) on average, with DAS of 1.9, 1.9 and 2.2 reported in the combination, etanercept-added and methotrexate-added groups, respectively (p<0.05 within group). Patients in the etanercept-added group achieved the greatest increase in DAS remission rates from the extension study baseline to week 52 (23.6% to 41.8%, p<0.01); patients in the combination (37.6% to 50.0%, p<0.01) and methotrexate-added (26.7% to 36.8%, p = NS) groups also demonstrated improvements. In addition, during the 52-week extension, combination treatment was associated with a favourable safety profile; no new unexpected safety signals or toxicities were observed. No cases of tuberculosis, opportunistic infections, systemic lupus erythematosus, or central demyelinating disorders occurred and serious infections were uncommon.[25]
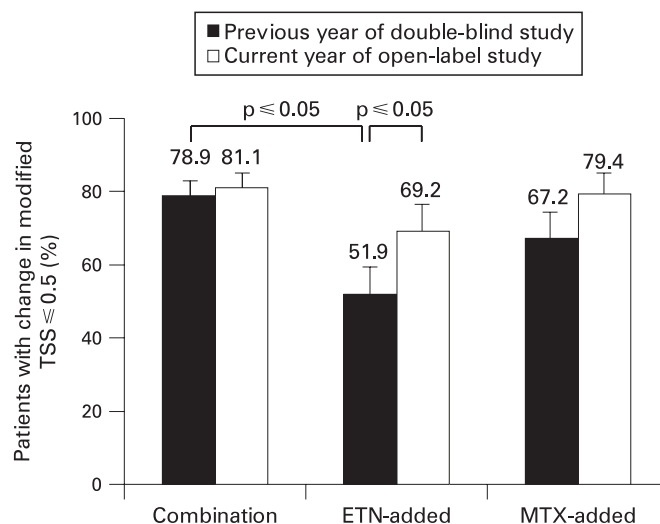
The results reported here indicate that 1 year of combination therapy can also provide additional radiographic improvement for patients with average moderate disease activity after 3 years of monotherapy. Moreover, continuation of combination therapy after 3 years of this regimen sustained or improved the prevention of radiographic progression from year 3 of the double-blind study to the end of the current 1-year study. Previous studies have shown that clinically relevant progression of joint damage can occur in patients with RA achieving persistent clinical remission with conventional DMARD therapy.[33 34] Similarly, in an analysis of the 3-year Trial of Etanercept and Methotrexate with Radiographic and Patient Outcomes (TEMPO) data, mean radiographic progression rates continued to increase, even in patients treated with methotrexate alone who were in clinical remission or who had very low disease activity.[35] Overall, however, increased radiographic progression was linked to increasing systemic inflammatory activity in those receiving methotrexate monotherapy. In contrast, patients treated with the combination of etanercept and methotrexate demonstrated inhibition of joint destruction independent of inflammatory activity. Moreover, even in patients with the lowest level of inflammation, progression of joint damage with combination therapy was at a significantly lower level than that with methotrexate alone. The radiographic progression that occurs despite good clinical response may support the need for more aggressive therapy than conventional DMARD. A more intensive therapeutic strategy could be considered to extend the standard of care beyond the control of disease activity to include radiographic non-progression and prevention of functional loss. The gain in long-term outcome in terms of function, ability to work and participation should be weighed against the extra costs involved in such a strategy.

The TEMPO study was the first to demonstrate that the combination of etanercept and methotrexate inhibits radiographic progression more than methotrexate or etanercept monotherapy. Although patients receiving etanercept and methotrexate monotherapies showed similar clinical improvement in both the second and third years of the double-blind

study, those receiving methotrexate monotherapy had greater increases in radiographic damage during these intervals.[18][30] In patients who received the methotrexate-only regimen for 3 years, adding etanercept for 1 year in this study significantly reduced the rate of radiographic progression; patients who had received etanercept monotherapy or combination therapy for 3 years demonstrated some reductions in radiographic progression during this year of combination therapy, although these changes were not significant. Whereas the rate of radiographic non-progression was significantly increased with the addition of etanercept in the methotrexate monotherapy group (69%), it ultimately did not reach the levels achieved in the groups that previously received either etanercept alone or in combination (79% and 81%, respectively). The observed difference in frequency of non-progression indicates that earlier use of combination etanercept–methotrexate treatment may provide a meaningful reduction in joint destruction compared with methotrexate alone.

Despite the minimal radiographic progression in all groups with combination therapy, treating patients for 3 years with methotrexate monotherapy before adding etanercept may have already led to some irreversible joint damage. For the methotrexate monotherapy group that added etanercept in this study, the mean radiographic progression was only +0.25 modified TSS units. However, during the last year of methotrexate monotherapy, the mean progression was +1.79 and during the first 2 years of methotrexate monotherapy in TEMPO, the mean progression was +3.34.[30] In contrast, the combination group demonstrated a mean progression of +0.24 in this study, compared with +0.42 in the last year and −0.56 in the first 2 years of TEMPO.[30] The composite mean progression after 3 years of treatment with methotrexate alone was +5.13, compared with +0.10 after 4 years of combination treatment with etanercept plus methotrexate. Although these data represent mean values for the two groups, it may be worth noting that, in individual patients, progression in modified TSS of more than 5 units with methotrexate monotherapy over 3 years represents a clinically important progression based on international expert panel findings.[36]

These radiographic results augment the previously reported clinical findings,[25] showing that patients who have improved from a mean of severe to moderate disease activity with methotrexate treatment continue to experience progressive radiographic damage that can be blocked by the addition of etanercept. Combination treatment with etanercept plus methotrexate provided enhanced protection against joint damage in patients with RA who had moderate disease activity despite monotherapy with either agent. Although all three groups showed some improvement, this benefit was particularly pronounced when etanercept was added to methotrexate monotherapy. The radiographic improvements achieved by patients treated with combination therapy for 3 years in the original double-blind study were sustained or improved during the fourth year of open-label treatment. The results of this study support the use of combination therapy with etanercept and methotrexate in patients with moderate disease on methotrexate monotherapy and suggest that earlier combination therapy could be considered in these patients.

Etanercept study 400 investigators: HD Bolosiu, Cluj-Napoca, Romania; J Brzezicki, Elblag, Poland; G-R Burmester, Berlin, Germany; B Canesi, Milano, Italy; H Chwalinska-Sadowska, Warszawa, Poland; C Codreanu, Bucuresti, Romania; M Cutolo, Genova, Italy; J de Melo Gomes, Lisboa, Portugal; A Filipowicz-Sosnowska, Warszawa, Poland; S Freiseleben-Sorensen, Copenhagen, Denmark; P Geusens, Diepenbeek, Belgium; JJ Gómez Reino, Santiago de Compostela, Spain; N Graudal, Herlev, Denmark; G Herrero-Beaumont, Madrid, Spain; M Janssen, Arnhem, The Netherlands; H Julkunen, Vantaa, Finland; J Kalden, Erlangen, Germany; J Kekow, Vogelsang, Germany; A Laffón, Madrid, Spain; H Lang, Plauen, Germany; P Lanting, Doetinchem, The Netherlands; R Luosujarvi, Kuopio, Finland; R Luukkainen, Satalinna, Finland; M Malaise, Liege, Belgium; E Martín Mola, Madrid, Spain; Z Mencel, Kalisz, Poland; C Montecucco, Pavia, Italy; K Pavelka, Prague, Czech Republic; A Perniok, Köln, Germany; F Radulescu, Bucuresti, Romania; R Sanmartí, Barcelona, Spain; L Settas, Thessaloniki, Greece; H Stehlikova, Ceska Lipa, Czech Republic; J Szechinski, Wroclaw, Poland; J Szerla, Krakow, Poland; C Tanasescu, Bucuresti, Romania; J Tornero, Guadalajara, Spain; S Transo, Jonkoping, Sweden; T Tuomiranta, Tampere, Finland; S Valtysdottir, Uppsala, Sweden; E Veys, Gent, Belgium; H Van den Brink, Alkmaar, The Netherlands; M Van de Laar, Enschede, The Netherlands; P Vitek, Zlin, Czech Republic; R Zahora, Terezin, Czech Republic.

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