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CONCISE REPORT

Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study

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ABSTRACT

Objective Assess golimumab efficacy/safety through 5 years in patients with active ankylosing spondylitis (AS).

Methods 356 patients with AS were randomly assigned to placebo, golimumab 50 mg or 100 mg every 4 weeks. At week 16, patients with inadequate response early escaped with blinded dose adjustments (placebo to 50 mg, 50 mg to 100 mg). At week 24, all patients receiving placebo crossed over to 50 mg. Blinded active therapy continued through week 104; from week 104 to week 252, the golimumab dose could be adjusted. Intent-to-treat and observed efficacy data were assessed by randomised treatment groups.

Results At week 256, and with >4.5 years of golimumab, overall intent-to-treat Assessment in SpondyloArthritis international Society criteria for 20% improvement (ASAS20) and ASAS40 response rates were 66.0% (235/356) and 57.0% (203/356), respectively; Bath AS Disease Activity Index 50% improvement response was 55.9% (199/356). Observed response rates among the 255 (72%) patients who continued golimumab through week 252 were consistent, albeit somewhat higher. Among patients who increased golimumab from 50 to 100 mg, 60.6% (20/33) and 44.7% (17/38) achieved ASAS20/ASAS40 responses, respectively, following ≥ 2 consecutive doses of golimumab 100 mg. Golimumab safety through week 268 was similar to that through week 24 regardless of dose.

Conclusions Clinical improvements observed in patients treated with golimumab through week 24 were sustained through week 256 (5 years). Long-term golimumab safety is consistent with that of other established tumour-necrosis-factor-antagonists.

Trial registration number ClinicalTrials.gov: NCT00265083.

Golimumab, a human monoclonal antibody to tumour necrosis factor (TNF)- α that is administered subcutaneously every 4 weeks, is approved for treating active ankylosing spondylitis (AS). We previously reported results of the double-blind, randomised, placebo-controlled, Phase 3 GO-RAISE study, in which golimumab was evaluated in patients with active AS, through week 24¹ and week 104² and now report findings through the completion of the 5-year GO-RAISE trial.

PATIENTS AND METHODS

Details of GO-RAISE patient eligibility criteria and study design have been reported¹ and are summarised

in the online supplement. Details of analyses specific to this 5-year report are also provided in the online supplement.^{3–12}

RESULTS**Patient disposition/characteristics and concomitant medications**

Among the 356 randomised patients, 355 received study treatment (figure 1). Baseline patient and disease characteristics,¹ as well as patient disposition through week 24¹ and week 104,² have been reported.

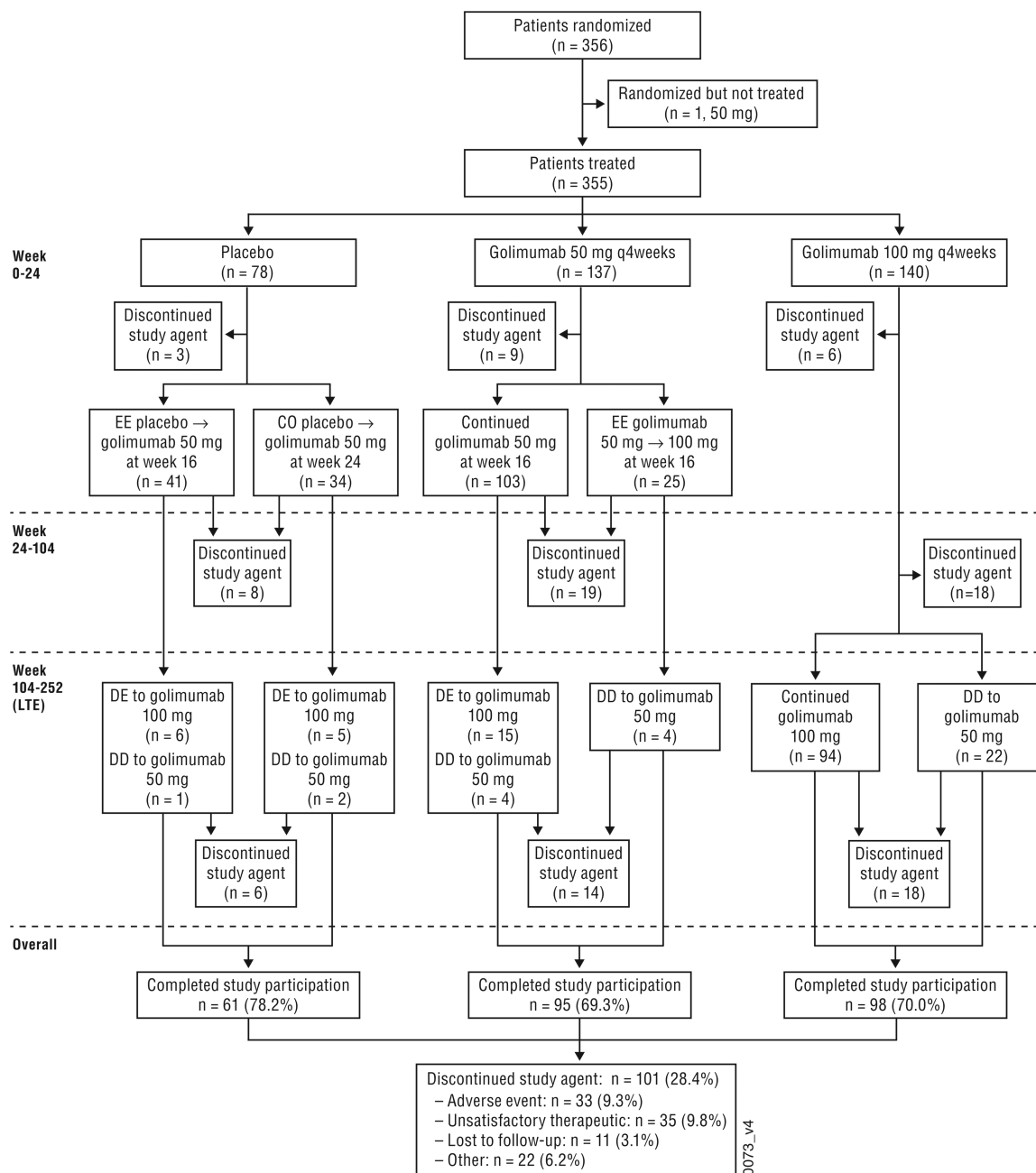
At week 16, 41 of 78 (52.6%) and 25 of 137 (18.2%) patients in Groups 1 and 2, respectively, had <20% improvement in total back pain and morning stiffness and entered early escape. Among the 355 treated patients, 101 (28.5%) discontinued study agent through week 252 (figure 1). Among patients who discontinued study agent due to adverse events (AEs), being lost to follow-up, or due to ‘other’ reasons, 51% achieved an Assessment in SpondyloArthritis international Society criteria for 20% improvement (ASAS20) response at the visit preceding discontinuation, versus 15% of patients who discontinued due to unsatisfactory therapeutic effect.

The proportion of patients using non-steroidal anti-inflammatory drugs declined from baseline to week 268 from 90% to 74% while that using disease-modifying antirheumatic drugs was relatively stable (32% to 36%) during the study.

Efficacy**Assessment in SpondyloArthritis international Society (ASAS) responses**

Results of intent-to-treat (ITT) analyses indicated that 220/356 (61.8%) and 166/356 (46.6%) patients achieved ASAS20 response and/or $\geq 40\%$ improvement (ASAS40) improvement, respectively, at week 24. At week 256, 235/356 (66.0%; 95% CI 61.1% to 70.9%) and 203/356 (57.0%; 95% CI 51.9% to 62.1%) patients achieved ASAS20 and/or ASAS40 response, respectively (figure 2A, B). ASAS partial remission (value <2 in each ASAS domain) was achieved by 121/356 (34.0%; 95% CI 29.1% to 38.9%) patients treated with golimumab at week 256 (figure 2C). Response rates were consistent, albeit somewhat higher, when assessed using observed data among patients who did not discontinue study participation by week 24 (see online supplementary figure S1A–C).

Based on observed data, 54 patients escalated the golimumab dose from 50 mg to 100 mg during the



CO = cross over DD = dose decreased DE = dose escalated EE = early escape LTE = long-term extension

Figure 1 Patient disposition through week 268.

trial. While 21 (38.9%) and 16 (29.6%) of these patients, respectively, achieved an ASAS20 or ASAS40 response before dose escalation, 33 and 38 patients, respectively, had not. Among these latter patients, 60.6% (20/33) achieved ASAS20 and 44.7% (17/38) achieved ASAS40 responses following ≥ 2 consecutive doses of golimumab 100 mg. Additional clinical findings are reported in the online supplement.

Health-related quality of life (HRQoL)

Mean changes from baseline in the physical component summary and mental component summary scores of the 36-item Short Form health survey indicated improvements in patients' HRQoL were sustained with up to 5 years of golimumab treatment (see online supplementary table S1). When assessed using ITT

analyses, 93/356 (26.1%; 95% CI 21.5% to 30.7%) and 180/356 (50.6%; 95% CI 45.4% to 55.8%) had achieved 36-item Short Form health survey physical component summary and mental component summary scores ≥ 50 , respectively, at week 256 (see online supplementary table S1). Findings were consistent with observed data (data not shown).

Antibodies to golimumab

Antibody-to-golimumab findings are reported in the online supplement.

Safety

Safety results through week 24¹ and week 104² were previously reported. Reported AEs from baseline through week 268 are

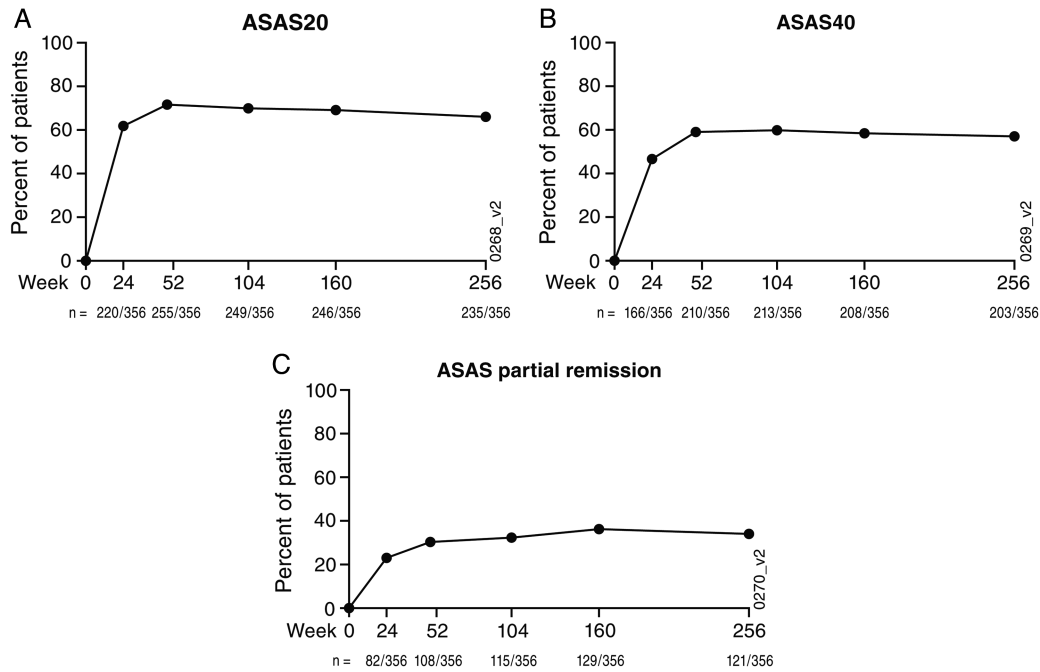


Figure 2 The proportions of patients in ASAS20 response (A), ASAS40 response (B), and/or ASAS partial remission (C) through week 256 based on intent-to-treat analyses. The placebo-controlled study period ended at week 24, but study participants and investigators remained blinded to the golimumab dose (50 mg or 100 mg) through week 100. During the long-term extension, which started with the week-104 golimumab injection, the investigator could increase or decrease the golimumab dose. ASAS20/40, $\geq 20\%/40\%$ improvement in the Assessment of SpondyloArthritis international Society (ASAS) criteria.

summarised in table 1 for patients who received ≥ 1 dose of golimumab through the first use of commercial biologics.

Through week 268, serious AEs were reported for 72 (20.4%) patients treated with golimumab (table 1), most commonly osteoarthritis requiring hospitalisation (2.0%), pneumonia (1.1%), worsening of AS (1.1%), and depression (1.1%). No increases in serious AEs were observed in successive years of golimumab treatment (see online supplementary table S2).

One (0.3%) patient, randomised to receive golimumab 50 mg, died from pancreatic cancer. This patient had also developed lymphoma after 3 years in the study and was receiving chemotherapy when the pancreatic cancer was discovered. The overall incidence of death for patients treated with golimumab was 0.07/100 patient-years (95% CI 0.00 to 0.38), with no difference observed between doses (table 1). In addition to the malignancies in one patient described above, two patients treated with golimumab had non-melanoma skin cancer (NMSC) through week 268, including one (1.3%) patient each receiving golimumab 50 mg and 100 mg and golimumab 100 mg only. For lymphoma, NMSC, other malignancies and all malignancies, the incidences per 100 patient-years did not appear to be dose-related (table 1). Similarly, the incidences of malignancies other than NMSC (excluded from the Surveillance, Epidemiology, and End Results database) were not elevated relative to those expected in the USA population (table 1). No overall increase in the incidence of malignancies was observed in successive years of golimumab treatment (see online supplementary table S2).

Serious infections were reported for 5.9% (21/353) of patients treated with golimumab through week 268. Pneumonia (four (1.1%) patients) was the only serious infection reported by more than one patient. The incidence of serious infections among patients receiving golimumab 100 mg appeared higher

than for patients receiving only golimumab 50 mg (table 1). No increase in serious infections was observed, however, in successive years of golimumab treatment (see online supplementary table S2).

DISCUSSION

Improvements in signs/symptoms, physical function, range of motion and HRQoL achieved at week 24¹ and sustained through week 104² of GO-RAISE were also sustained with up to 5 years of golimumab treatment of patients with AS. While findings were generally similar between the golimumab doses, this is the first report to assess the effects of a dose increase in patients with AS who had inadequate response to golimumab 50 mg. When investigators were allowed to increase the dose in consultation with their patients for lack of efficacy, 61% of patients gained ASAS20 response. While the golimumab dose approved for the treatment of active AS is 50 mg, this is an important finding that reflects a scenario likely to be encountered in clinical practice. Results of the recently published certolizumab trial in axial spondyloarthritis, which compared the same cumulative dose given at two different dosing intervals (200 mg every 2 weeks and 400 mg every 4 weeks), indicated very similar efficacy.¹³ Thus, to our knowledge, GO-RAISE is the only large prospective trial of a TNF-inhibitor in AS comparing two different doses and showing a dose response in patients who have inadequate response to the lower dose. Similar findings have been reported in patients with rheumatoid arthritis.¹⁴

Approximately a fifth of the 255 patients who participated in the long-term extension did not achieve an ASAS20 response at 5 years, yet they continued to receive golimumab and completed the trial, which is consistent with results observed through

Table 1 Summary of AEs through week 268

	GLM 50 mg only	GLM 50 mg and 100 mg	GLM 100 mg only	All GLM patients
No. of patients	158	77	118	353
Mean weeks of follow-up	207.6	232.2	213.0	214.8
Pts with AE(s)	153 (96.8%)	76 (98.7%)	115 (97.5%)	344 (97.5%)
Pts who died	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Incidence/100 pt-yrs* (Exact 95% CI)	0.16 (0.00 to 0.88)	0.00 (0.00 to 0.87)	0.00 (0.00 to 0.62)	0.07 (0.00 to 0.38)
Pts with serious AE(s)	27 (17.1%)	19 (24.7%)	26 (22.0%)	72 (20.4%)
Pts who discontinued study agent due to AE(s)	12 (7.6%)	6 (7.8%)	14 (11.9%)	32 (9.1%)
Pts with malignancy†	1 (0.6%)	1 (1.3%)	1 (0.8%)	3 (0.8%)
Incidence/100 pt-yrs (Exact 95% CI)	0.16 (0.00 to 0.88)	0.29 (0.01 to 1.63)	0.21 (0.01 to 1.16)	0.21 (0.04 to 0.60)
SIR—observed/SEER (Exact 95% CI)	0.58 (0.01 to 3.21)	0.00 (0.00 to 1.77)	0.00 (0.00 to 2.37)	0.21 (0.01 to 1.19)
<i>Lymphoma‡</i>	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Incidence/100 pt-yrs (Exact 95% CI)	0.16 (0.00 to 0.88)	0.00 (0.00 to 0.87)	0.00 (0.00 to 0.62)	0.07 (0.00 to 0.38)
SIR—observed/SEER (Exact 95% CI)	9.67 (0.24 to 53.90)	0.00 (0.00 to 35.60)	0.00 (0.00 to 39.68)	3.80 (0.10 to 21.18)
<i>NMSC§</i>	0 (0.0%)	1 (1.3%)	1 (0.8%)	2 (0.6%)
Incidence/100 pt-yrs (Exact 95% CI)	0.00 (0.00 to 0.47)	0.29 (0.01 to 1.63)	0.21 (0.01 to 1.16)	0.14 (0.02 to 0.50)
<i>Other malignancies¶</i>	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Incidence/100 pt-yrs (Exact 95% CI)	0.16 (0.00 to 0.88)	0.00 (0.00 to 0.87)	0.00 (0.00 to 0.62)	0.07 (0.00 to 0.38)
SIR—observed/SEER (Exact 95% CI)	0.61 (0.02 to 3.39)	0.00 (0.00 to 1.85)	0.00 (0.00 to 2.52)	0.22 (0.01 to 1.25)
Pts with serious infection(s)	6 (3.8%)	8 (10.4%)	7 (5.9%)	21 (5.9%)
Incidence/100 pt-yrs** (Exact 95% CI)	1.27 (0.55 to 2.50)	3.49 (1.80 to 6.10)	2.28 (1.14 to 4.07)	2.13 (1.44 to 3.02)
Pts with injection-site reaction(s)	17 (10.8%)	13 (16.9%)	13 (11.0%)	43 (12.2%)

Data presented are n (%) unless indicated otherwise.

*Incidence/100 pt-yrs (Exact 95% CI) of death for placebo through week 24=0.00 (0.00 to 10.42).

†Incidence/100 pt-yrs (Exact 95% CI) of all malignancies for placebo through week 24=3.50 (0.09 to 19.48); SIR (Exact 95% CI)=0.00 (0.00 to 33.37).

‡Incidence/100 pt-yrs (Exact 95% CI) of lymphoma for placebo through week 24=0.00 (0.00 to 10.42); SIR (Exact 95% CI)=0.00 (0.00 to 582.38).

§Incidence/100 pt-yrs (Exact 95% CI) of NMSC for placebo through week 24=3.50 (0.09 to 19.48).

¶Incidence/100 pt-yrs (Exact 95% CI) of other malignancies for placebo through week 24=0.00 (0.00 to 10.42); SIR (Exact 95% CI)=0.00 (0.00 to 35.31).

**Incidence/100 pt-yrs (Exact 95% CI) of serious infections for placebo through week 24=3.48 (0.09 to 19.39).

AE, adverse event; GLM, golimumab; NMSC, non-melanoma skin cancer; no., number; pts, patients; pt-yrs, patient-years; SEER, Surveillance, Epidemiology and End Results database; SIR, standardised incidence ratio.

>3 years of etanercept¹⁵ and 5 years of adalimumab¹⁶ in patients with AS. Thus, while ASAS20 response is a validated composite measure of patient outcome, it may not include all aspects of improvement important to patients. Also, while 20% improvement in symptoms is the lowest level acceptable to a clinician to indicate efficacy, an individual patient may consider a different level of improvement acceptable to continue that therapy. Indeed, we determined that even though these patients were deriving <20% relief in their night-time pain, overall back pain, and sleep improvement, their cumulative improvement was enough for them to elect study continuation. Since treatment with TNF-inhibitors can be costly, recommendations on the expected minimal therapeutic response for such agents have been published by independent organisations such as ASAS. These recommendations include assessment of response based on one outcome measure, plus expert opinion, for continuation of treatment. Our results, as well as those observed with other agents, suggest that there is apparent benefit, including improved performance-based physical function in ASAS20 non-responders, experienced by patients that is not captured by a single measure.^{15–17} Hence, other tertiary end points or patient-reported outcomes should be considered in future research of treatment persistence.

The golimumab safety profile through week 268 was consistent with those previously reported.^{1 2} Importantly, no increases in serious AEs, malignancies, serious infection or injection-site reactions were observed in successive years of golimumab treatment.

While efficacy analyses were performed using a conservative ITT approach, and consistency was observed between the ITT and observed data analyses, the findings reported here remain limited by several factors. It is important to note that no patients received placebo, and thus there is no control group, after week 24. Also, the study was blinded through the week 100 database lock, but open label from that point forward. Changes to the golimumab dose from 50 mg to 100 mg or from 100 mg to 50 mg during the study extension were at the discretion of the investigator. Thus, since dose escalation was uncontrolled, conclusions related to dose change are limited. Additionally, while long-term efficacy and safety have been observed over 5 years, long-term effectiveness in the context of cost-effectiveness requires evaluation using real-world data in patients with AS treated with golimumab.

Taken together, results reported here indicate that clinical improvements observed in patients with AS treated with golimumab through week 24 were sustained through up to 5 years of treatment. Importantly, no new safety signals were detected, and the golimumab benefit-risk profile remains positive.

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Competing interests JB has received honoraria for talks, advisory boards and grants for studies from Celltrion, Amgen, Abbott, Roche, BMS, Janssen, Novartis, Pfizer (Wyeth), MSD (Schering-Plough), Sanofi-Aventis and UCB. AD has received payments for educational lectures, teleconferences and serving on advisory boards for Janssen. This potential conflict of interest has been reviewed and managed by OHSU. RDI has received consulting fees from Merck, Schering-Plough, Abbott, Amgen and Sanofi-Aventis. DvdH has received funding from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Chugai, Covagen, Daiichi, Eli-Lilly, GSK, Janssen Biologicals, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB and Vertex and is Director of Imaging Rheumatology BV. YZ, SX, CH and BH are employees of Janssen R&D, a Johnson & Johnson pharmaceutical company, and own stock and/or stock options in Johnson & Johnson.

Ethics approval Approved by the Institutional Review Board/Independent Ethics Committee Governing each site.

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REFERENCES

- Inman RD, Davis JC Jr, van der Heijde D, *et al.* Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008;58:3402–12.
- Braun J, Deodhar A, Inman RD, *et al.* Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis* 2012;71:661–7.
- van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361–8.
- Garrett S, Jenkinson T, Kennedy LG, *et al.* A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.
- Calin A, Garrett S, Whitelock H, *et al.* A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281–5.
- Jenkinson TR, Mallorie PA, Whitelock HC, *et al.* Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994;21:1694–8.
- van der Heijde D, Landewe R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. *Ann Rheum Dis* 2008;67:489–93.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- Zhou H, Jang H, Fleischmann RM, *et al.* Pharmacokinetics and safety of golimumab, a fully human anti-TNF- α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007;47:383–96.
- Braun J, Baraliakos X, Hermann KG, *et al.* Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo-controlled GO-RAISE study. *Ann Rheum Dis* 2012;71:878–84.
- Braun J, Baraliakos X, Hermann K-G, *et al.* The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. *Ann Rheum Dis* 2014;73:1107–13.
- National Cancer Institute. The Surveillance, Epidemiology, and End Results (SEER). 2004. <http://seer.cancer.gov>
- Landewé R, Braun J, Deodhar A, *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014;73:39–47.
- Lutt JR, Deodhar A. Rheumatoid arthritis: strategies in the management of patients showing an inadequate response to TNF α antagonists. *Drugs* 2008;68:591–606.
- Davis JC Jr, van der Heijde DM, Braun J, *et al.* Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008;67:346–52.
- Sieper J, van der Heijde D, Dougados M, *et al.* Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;71:700–6.
- van Weely SF, van Denderen JC, Steultjens MP, *et al.* What do we miss? ASAS non-responders on anti-TNF therapy show improvement in performance-based physical function. *Rheumatology (Oxford)* 2013;52:1884–9.