Online supplementary Table 1: the search strategy for the systematic literature review (SLR) to identify flare definitions used in axSpA studies

Overview	The SLR was conducted in 2 phases. The 1st phase was focused on all randomized controlled trials (RCTs) of NSAIDs or antiTNF in axial SpA patients. The 2nd phase consisted on a research of specifically flares-centered studies in axial SpA.
Data Sources and Searches step 1: RCTs	All the RCTs and quasi RCTs using NSAIDs or antiTNF in axial SpA patients were reviewed. First, 2 recent SLRs concerning NSAIDs in axial SpA (REF 1) and concerning antiTNF in axial SpA (REF 2) whatever the control group were used. These SLRs included articles published up to June 2013. They both included data from MEDLINE and EMBASE , and the one concerning NSAIDs was also performed in Cochrane, DARE (Database of Abstracts of review of Effects), HTA (Health Technology Assessment) database, clinicaltrials.gov, WHO (World Health Organization), ICTRP (International Clinical Trials Registry Platform) and in the websites of the regulatory agencies (e.g. the US Food and Drug Administration (FDA) MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm), the European Medicines Evaluation Agency (http://www.ema.europa.eu), the Australian Adverse Drug Reactions Bulletin (http://www.tga.gov.au/safety/ews-monitoring.htm), and the UK Medicines and Healthcare products Regulatory Agency pharmacovigilance and drug safety updates (http://www.mhra.gov.uk/Safetyinformation/index.htm). These data were updated up to May 2014 using PUBMED, EMBASE, Cochrane, clinicaltrials.gov, and congress abstracts from EULAR and ACR (2012-2014). The language was limited to English, German, French and Spanish. For the data from June 2013 to May 2014, the following keywords were used : ("Spondylitis, Ankylosing" [Mesh] OR ankylosing spondylitis [tw]) AND (clinical trials [tw] OR clinical trial [tw] OR "Clinical Trial" [Publication Type])for PUBMED, and ('ankylosing spondylitis'/exp/mj OR 'ankylosing spondylitis' AND ('disease exacerbation'/exp OR 'disease exacerbation') AND ('clinical trial'/exp OR 'clinical trial') for EMBASE, and (ankylosing spondylitis) for clinical trials.gov and Cochrane.
Data Sources and Searches step 2: Flares-centered studies	Then, all the articles concerning flares in axial SpA in PUBMED and EMBASE were reviewed, with no limit of dates. The language was limited to English, German, French and Spanish. For this step we used the following key words: The language was limited to English, German, French and Spanish. The following key words were used: ("Spondylitis, Ankylosing" [Mesh] OR ankylosing spondylitis [tw]) AND (flares [tw] OR flare [tw] OR exacerbation [tw] OR relapse [tw] OR recurrence [Mesh] OR recurrence [tw] OR clinical reactivation [tw]) for PUBMED , and we used successively the 2 list of key words for EMBASE: ('ankylosing spondylitis'/exp/mj AND ('disease exacerbation'/exp OR 'flare' OR 'flares' OR 'relapse'/exp OR 'recurrent disease'/exp) NOT 'clinical trial'/exp), and ('ankylosing spondylitis'/exp/mj OR 'ankylosing spondylitis'/exp OR

	'ankylosing spondylitis' AND ('disease exacerbation'/exp OR 'disease exacerbation' OR 'relapse'/exp OR 'relapse' OR 'recurrence'/exp OR 'recurrence').
Study selection	For data collection and analysis, one author (AD) assessed independently each title and abstract for suitability for inclusion in the review. If there was any doubt, the full text article was retrieved. Articles were included only if there were RCTs or flares-centered studies with a definition of flare. To be included, RCTs had to concern patients 16 years of age or older with axial SpA whatever the diagnosis/classification criteria. Publications concerning trials already published and included, were excluded from analysis. Studies with the term flares but without definitions of flares, or without full text (e.g. only abstract) or duplicate articles (e.g. already included in the 1st step of SLR) were excluded.
Data extraction	For data extraction, one author (AD) extracted general data and specific data for flares. General data were study identification (first author, journal, year of publication), study characteristics (RCT or other trial intervention, control group, geographical area, sample size, duration of follow-up, criteria for axSpA diagnosis), patient characteristics (average age of patients, percentage of women, percentage of HLA-B27-positive patients, mean disease duration of AxSpA (years since diagnosis), percentage of patients with New York modified criteria, mean BASDAI at baseline). Specific flare data were: the flare design (flare design trial or flare discontinuation trial), the term used for flare (e.g. relapse, recurrence, exacerbation), the origin of the definition (arbitrary or consensual), and the exact definition for flare with: the instrument used, the cutoff, if it was a combination of several instruments or one instrument only, and if it was a relative or absolute change or an absolute value. Then, if possible the number of patients concerned by the definition of flare in the trial was extracted.
Data synthesis and analysis	Analysis was descriptive and included the instrument used to define flare, use of one instrument or of a combination, cutoff used to determine flare, use of a relative or absolute change or use of an absolute value. All the data concerning definitions of flares were classified: word used for “flare”, instrument used to define flare, use of one instrument or of a combination, cutoff used to determine flare, use of a relative or absolute change or an absolute value.

1: Kroon FP, van der Burg LR, Ramiro S, Landewé RB, Buchbinder R, Falzon L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev. 2015;7:CD010952.

2: Bautista-Molano W, Navarro-Compán V, Landewé RBM, Boers M, Kirkham JJ, van der Heijde D. How well are the ASAS/OMERACT Core Outcome Sets for Ankylosing Spondylitis implemented in randomized clinical trials? A systematic literature review. Clin Rheumatol. 2014 Sep;33(9):1313–22.

Online supplementary Table 2: the 38 manuscripts (with the 38 corresponding references) with the definition of flares used and where available, the % of flares in the study

1st author (year) [REF]	Type of study	Drug assessed/ control	Flare design / Flare discontinuation	Sample size (randomized patients)	% males	Age, years (Mean)	Timeframe of flare definition	Definition of flare used	% patients in flare
Mena (1977, South med J) [1]	RCT	NSAID / NSAID	Flare design	26	NA	NA	6 weeks	clear increase in spinal or SI pain and ≥1 of the criteria: muscle spasm in back/decreased range of motion of some part of the spine/increased ESR	NA
Mena (1977) [2]	RCT	NSAID/ phenylbutazone	Flare design	26	NA	NA	6 weeks	clear increase in spinal or SI pain and ≥1 of the criteria: muscle spasm in back/decreased range of motion of some part of the spine/increased ESR	NA
Ansell (1978) [3]	RCT	NSAID / NSAID	Flare design	25	8%	NA	2 weeks	deterioration in at least 2 criteria among: morning stiffness, immobility stiffness, morning pain,	NA

								discomfort, Schober, wall tragus distance	
Bryon (1982) [4]	RCT	NSAID / tolmetin sodium	Flare design	34	22%	43.6	4 weeks	deterioration of at least 2 of these criteria: pain on spinal palpation/morning stiffness/nocturnal pain/subjective pain/immobility stiffness	86%
Fransen (1986) [5]	RCT	NSAID/ phenylbutazone	Flare design	246	0%	37	14 days	a worsening of patient's condition in which pain and stiffness was an essential component requiring treatment	NA
Khan (1987) [6]	RCT	NSAID/ NSAID	Flare design	262	16%	NA [19-67]	2-15 days	2 criteria among: 1 point increase in cervical/thoracic/lumbar/SI pain on a 0-4 point scale assessed by patient and ≥2 of criteria: increased duration of morning stiffness (≥30 min)/decreased shober (≥1 cm)/decreased chest expansion (≥1 cm)/increased	NA

								distance fingertips to floor (≥5cm)/≥1 periph joint affected by swelling and tenderness/ESR ≥28mm	
Schwarzer (1990) [7]	RCT	NSAID /NSAID	Flare design	24	12%	41	3 days	increase in back pain and stiffness	NA
Dougados (1994) [8]	RCT	NSAID / placebo	Flare design	285	26%	40	2 days	pain > 40mm on VAS 100mm and increase in pain of at least 30% between the screening and the entry visit	90%
Dougados (1999) [9]	RCT	NSAID / placebo	Flare design	473	22%	32.5	2-15 days	pain ≥40mm on VAS 100mm and an increase at least 30% between the screening visit	91%
Ruof (1999) [10]	Non randomized controlled trial	NSAID / vitamin / placebo	Flare discontinuation	120	25%	44	NA	predefined magnitude and duration of deterioration in back pain	NA
Dougados (2001) [11]	RCT	NSAID / placebo	Flare design	246	31%	38.6	14 days	pain scored ≥40 mm on VAS 100mm and an increase of at least 30% between the screening and the baseline visit	31%

Breban (2002) [12]	Open study	antiTNF	Flare discontinuation	50	24%	35	NA	≥50% loss of global assessment of pain	NA
Baraliakos (2005) (outcome…) [13]	Open extension study	Anti TNF	Flare discontinuation	26	23%	37.1	NA	BASDAI ≥4 and physician global assessment ≥4	NA
Baraliakos (2005)(clinical response…) [14]	Open extension trial	Anti TNF	Flare discontinuation	42	NA	NA	NA	BASDAI ≥4 and physician global assessment ≥4	NA
Brandt (2005) [15]	Open observational study	Anti TNF	Flare discontinuation	26	23%	37.1	NA	BASDAI ≥4 and physician global assessment ≥4	NA
Van der Heijde (2005) [16]	RCT	NSAID / NSAID	Flare design	387	22%	43.6	NA	worsening of AS defined as ≥40mm on patient's assessment of spine pain and an increase of ≥30% (min 12mm)compared with screening period	NA
Wanders (2005) [17]	RCT	NSAID / NSAID	Flare design	215	31%	38.5	NA	pain≥ 40mm and increase ≥30%	NA
Barkhuizen (2006) [18]	RCT	NSAID/ placebo	Flare design	611	26%	44.5	2 weeks	pain on VAS≥50 mm worsening by 30% compared with the	NA

								preinclusion visit	
Boonen (2006) [19]	Observational	antiTNF	Cost utility	130	29%	45.9	NA	BASDAI≥4	NA
Baraliakos (2007) [20]	Extension study	Anti TNF	Flare discontinuation	NA	NA	NA	NA	BASDAI ≥4 and physician global assessment ≥4	NA
Huang (2007) [21]	Open study	Anti TNF	Flare discontinuation	63	37%	32.8	NA	BASDAI >60% of the corresponding score at baseline	NA
Breban (2008) [22]	RCT	Anti TNF/ anti TNF	Flare discontinuation	247	24%	41	NA	a negative answer to the 1st question ("since the last connection, did you think that your disease has remained under control?") and a positive answer to the 2nd question ("since…, do you think that your disease has been worsening?") and either an increase in BASDAI score of ≥1/10 or an increase in patient's assessment of ≥2/10 compared with the lowest score reached by the patient since	NA

								the 1st infliximab infusion	
Sieper (2008) [23]	RCT	NSAID/ NSAID	Flare design	458	31%	44.8	2-14 days	pain≥ 40mm and increase ≥30%	NA
Krzysiek (2009) [24]	RCT	antiTNF	Flare discontinuation	169	23%	40	NA	negative response at "since the last connection, do you thinck that your disease has remained under control?"AND a positive question at ""do you think that your disease has been worsening?" AND either an increase in BASDAI score ≥1 or an increase in global pain score ≥2 as compared with the lowest score reached by that patient since the 1st infusion.	NA
Baraliakos (2010) [25]	review	Anti TNF	NA	NA	NA	NA	NA	BASDAI ≥4 and physician global assessment ≥4	NA
Maksymowych (2010) [26]	Not interventional study	NA	NA	291	25%	45.7		2 questions: “Are you currently experiencing a flare of your AS?” and “Is your AS	49%

								sufficiently active to require an assessment and examination from your rheumatologist?”	
Heldmann (2011) [27]	Open study	Anti TNF	Flare discontinuation	103	17%	44	NA	BASDAI> 4 and physician's global assessment > 4 at screening and baseline	NA
Gratacós Jordi (2012) [28]	RCT	AntiTNF	Flare discontinuation	NA	NA	NA	NA	BASDAI > 4, global clinical impression by physician >4 and at least one of three following criteria: patient impression >= 4, axial nocturnal pain (VAS) >= 4, and increased of acute phase reactants (reactive C protein (PCR) and/or erythrocyte sedimentation rate (ESR))	NA
Song (2012) [29]	Open study	Anti TNF	Flare discontinuation	17	29%	NA	NA	BASDAI increase of 2 points	NA
Cantini (2013) [30]	RCT	Anti TNF/ anti TNF	Flare discontinuati	78	28%	38	NA	BASDAI > 4 or any of the other above-	NA

			on					mentioned peripheral articular and extra-articular manifestations independently of elevation of acute-phase reactants	
Deng (2013) [31]	RCT	Thalidomide /SLZ / NSAID	Flare design	111	NA	NA	NA	increase of BASDAI ≥2 or BASDAI degradation≥80%	NA
Haibel (2013) [32]	RCT	AntiTNF	Flare discontinuation	24	54%	37.5	NA	loss of an established ASAS40 response as compared to baseline at any timepoint	NA
Jaclyn K Anderson (2013) [33]	RCT	Anti TNF/ placebo	Flare discontinuation	NA	NA	NA	NA	2 consecutive study visits with ASDAS ≥ 2.1	NA
Song (2013) [34]	Open study	Rituximab	Flare discontinuation	9	NA	NA	NA	1,5 point worsening of the BASDAI compared to the lowest BASDAI	NA
Kadar (2014) [35]	Retrospective	NA	NA	17	NA	46	Between 2 visits	when the disease activity assessed by BASDAI became high from low or moderate activity at the previous visit	50%
Sieper (2014)	RCT	Anti TNF/	Flare design	158	28%	31.4	NA	increase in total back	NA

(INFAST part1) [36]		placebo						pain≥30%	
Sieper (2014) (INFAST part 2) [37]	RCT	NSAID/ placebo	Flare design	82	22%	29	2 consecutive visits within 1-3 weeks of each other	BASDAI (0-10) ≥3 cm	7%
Dougados (2014) [38]	RCT	AntiTNF/placebo	Flare design	90	38%	39	NA	Symptom flare	70%

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Online supplementary Table 3. The methods used in the vignette exercise and examples of vignettes

Development of the case-vignettes	The case-vignettes were elaborated by 3 authors (AD, LG and MD) during a meeting (July 16th 2014). A vignette is a "brief written case history of a fictitious patient based on a realistic clinical situation that is accompanied by 1 or more questions that explore what a physician would do if presented with the actual patient". (Veloski 2005). Vignettes should be realistic, brief and precise. It was decided to have the vignettes only in English.
Scenario	In this study, only one scenario was used for all the vignettes. "A 32 year-old man with a well-established diagnosis of axial SpA consults you at 2 successive timepoints. In comparison to the previous visit and according to the following data, and all other things being equal (physical examination, CRP and NSAID intake), do you consider this patient is flaring at the second visit? Yes or No. Please give an answer (yes or no) even if you are unsure." It was decided that a single phenotype of axial SpA would be proposed in the scenario, excluding potential signs of fibromyalgia or peripheral SpA, in order to avoid an excessive number of vignettes, and considering that defining flares in fibromyalgia is not our objective. The disease duration was not given since we aimed for a flare definition which would not depend on disease duration. The timeframe between visits was not determined to allow better external validity of the definition.
Variations in the vignettes	For each case-vignette, different values of instruments used to define flares were proposed by the authors. It was decided that vignettes would describe variations of one instrument only, and not a combination of variations of several instruments, i.e., "all other things being equal". The vignettes did not give any information other than the variable of interest. For each question, participants chose the "yes" or "no" answer. No other answer was possible.
Selection of relevant domains for vignettes	Instruments used in case-vignettes to assess flares in axial SpA were chosen as: ✓ BASDAI on a numeric rating scale (0-10) ✓ Pain due to axial SpA on a numeric rating scale (0-10) ✓ ASDAS score ✓ Initially, CRP and NSAID intake BASDAI and pain were selected because there were the 2 most frequent instruments in the literature used to define flares in axial SpA. ASDAS score was selected, because this is a recent instrument validated in axial SpA by ASAS. CRP was selected because a number of studies used this instrument to assess flares in axial SpA.

	NSAID intake was selected, because NSAIDs represent a treatment of short term efficacy useful in daily practice when a disease exacerbation exists. Thus, an increase of NSAIDs intake could reflect a flare of axial SpA.
Variations of outcomes values	It was decided that BASDAI and pain could vary only by a minimum of 1/10 on NRS (Numeric Rating Scale). Minimal initial BASDAI and initial pain were 0, and maximal initial BASDAI and pain were 6 (higher baseline values were excluded, because referring to a non-controlled disease). Variations of ASDAS were decided taking into account minimal clinically important differences for this score. Variations of CRP were arbitrarily decided with steps of 5, 10, 20, 30, with initial values of: <5, 8, 13, 18, and 25 mg/l. NSAIDs intake was assessed using one NSAID, Naproxen, with no intake or intake of half dose (500mg per day) or full dose (1000mg per day). Initial frequencies of intake were: no intake, intake <1 day/ week, 1 to 3 days/week, 3 to 5 days/week, ≥5 days, and only for the 500mg dosage: everyday. Final frequencies of intake could be: intake <1 day/week, 1 to 3 days/week, 3 to 5 days/week, ≥5 days/week, every day (7 days/week).
Sending out the vignettes to the ASAS members	All the 159 ASAS experts were asked to assess a sample of 46 vignettes between July and December 2014; each sample was intentionally constructed to include vignettes for each outcome and a distribution of changes in status. The choice of vignettes' attribution was different for each ASAS member, and comprised 5 vignettes concerning each outcome for the first round, and 21 additional vignettes for the second round. The attributions were made using excel and included a good spread between different variations for each participant (to make sure one person did not receive only vignettes with changes of one point for each outcome for example).
Covering email and instructions used for the vignette exercise	Dear ASAS member, This email is to ask for your participation in an ASAS project. This ASAS project aims to find a consensual definition of flare in axial SpA to be used in the context of clinical trials and longitudinal studies. This project is led by Maxime Dougados and is endorsed by the ASAS Executive. We remind you it was presented during the ASAS sessions last January and then in June during the EULAR congress. As an ASAS member, we count on your participation and we kindly remind you that participation in ASAS initiatives is part of being an ASAS member. For this initiative, you are invited to answer to case-vignettes concerning flares in axial SpA. You have been attributed 25 case-vignettes for which your answer is required as 'flare yes/no'. The exercise is very quick; it will take you no more than 5-10 minutes to answer. Please find attached an Excel file including the scenario and different vignettes. Please save the file to your computer, complete the column about flares yes/no and please send it back to us or use 'reply' to this email. Please can we ask you to send your answer within 2 weeks.

	Thank you for your participation, Best wishes There were no instructions regarding what should be defined as a “flare”. The document opened onto this text : for this initiative, you are invited to answer to case-vignettes concerning flares in axial SpA. You have been attributed 25 case-vignettes for which your answer is required as ‘flare yes/no’. Please select in each of these cases if the patient is flaring at the second visit, yes or no.
Vignette example for Pain	A 32 year-old man with a well-established diagnosis of axial SpA consults you at 2 successive timepoints. In comparison to the previous visit and according to the following data, and all other things being equal (physical examination, CRP and NSAID intake), do you consider this patient is flaring at the second visit? Yes or No. Please give an answer (yes or no) even if you are unsure. - Initial (first visit) Pain score (0-10 NRS): 3 - Final (second visit) Pain score (0-10 NRS): 7 - Flare: Yes/No Reminder. Pain due to axial SpA is assessed as follows: "Circle the number between 0 and 10 that best describes the pain you felt due to spondyloarthritis during the last 48 hours". Interpretation: Pain levels below 4 are usually considered acceptable.
Vignette example for BASDAI	A 32 year-old man with a well-established diagnosis of axial SpA consults you at 2 successive timepoints. In comparison to the previous visit and according to the following data, and all other things being equal (physical examination, CRP and NSAID intake), do you consider this patient is flaring at the second visit? Yes or No. Please give an answer (yes or no) even if you are unsure. - Initial (first visit) BASDAI (0-10): 2 - Final (second visit) BASDAI (0-10): 4 - Flare: Yes/No Reminder. The BASDAI takes into account axial, peripheral and entheseal pain, fatigue and morning stiffness. Interpretation: an active disease is defined by a BASDAI ≥4/10, and an improvement of 2 points on BASDAI is the minimal clinically important improvement. There is no definition of the minimal clinically important worsening/deterioration.

Vignette example for ASDAS-CRP	A 32 year-old man with a well-established diagnosis of axial SpA consults you at 2 successive timepoints. In comparison to the previous visit and according to the following data, and all other things being equal (physical examination, CRP and NSAID intake), do you consider this patient is flaring? Yes or No. Please give an answer (yes or no) even if you are unsure - Initial ASDAS score: 0.8 - Final ASDAS score : 2.3 - Flare: Yes/No Reminder. The ASDAS score takes into account back pain, duration of morning stiffness, patient global assessment, peripheral pain/ swelling and CRP. Interpretation: an ASDAS score<1.3 defines an inactive disease, an ASDAS score between 1.3 and 2.1 corresponds to a moderate disease activity, an ASDAS score between 2.1 and 3.5 reflects a high disease activity, and an ASDAS sore above 3.5 corresponds to a very high disease activity. An improvement of 1.1 on ASDAS score defines a clinically important improvement. There is no definition of the minimal clinically important worsening/deterioration.

Supplementary online figure 1. The ROC curves for each outcome to determine flares.

Figure A. ROC curve to define flares based on changes in pain

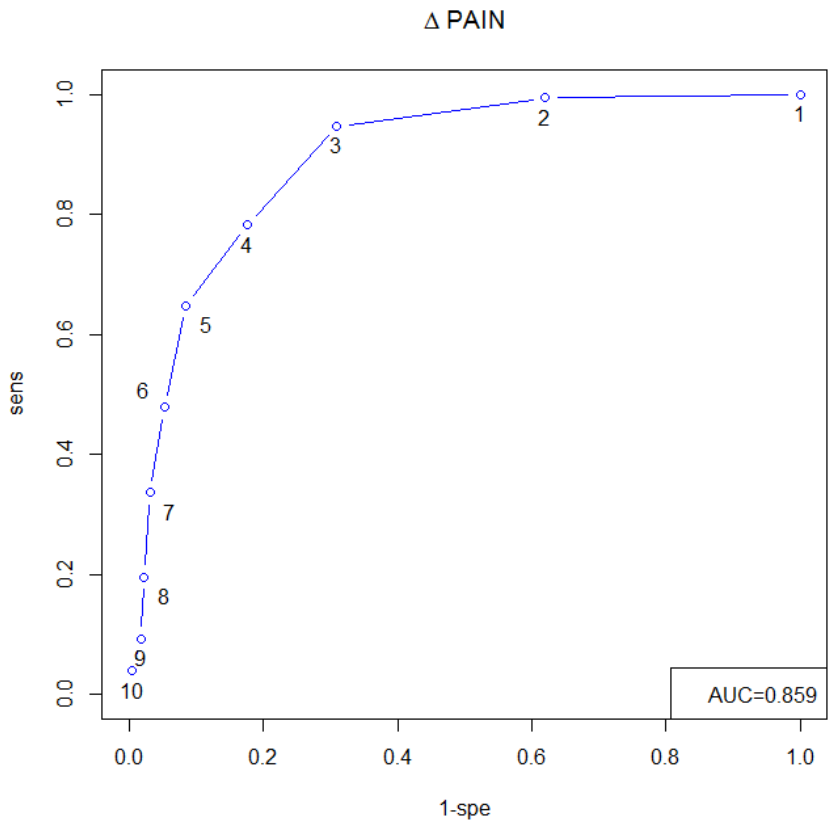

Figure B. ROC curve to define flares based on changes in BASDAI

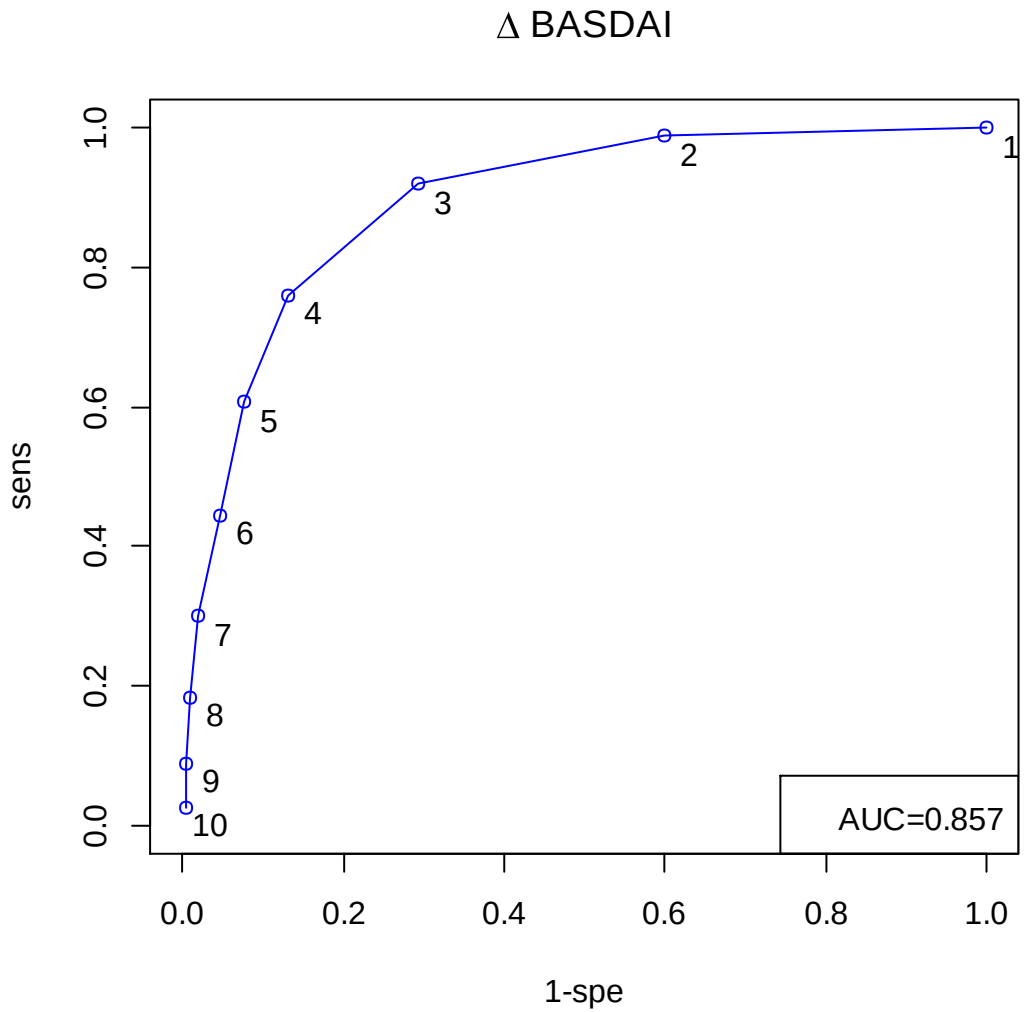

Figure C. ROC curve to define flares based on changes in ASDAS CRP