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Update of the literature review on the treatment with biologics as basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis

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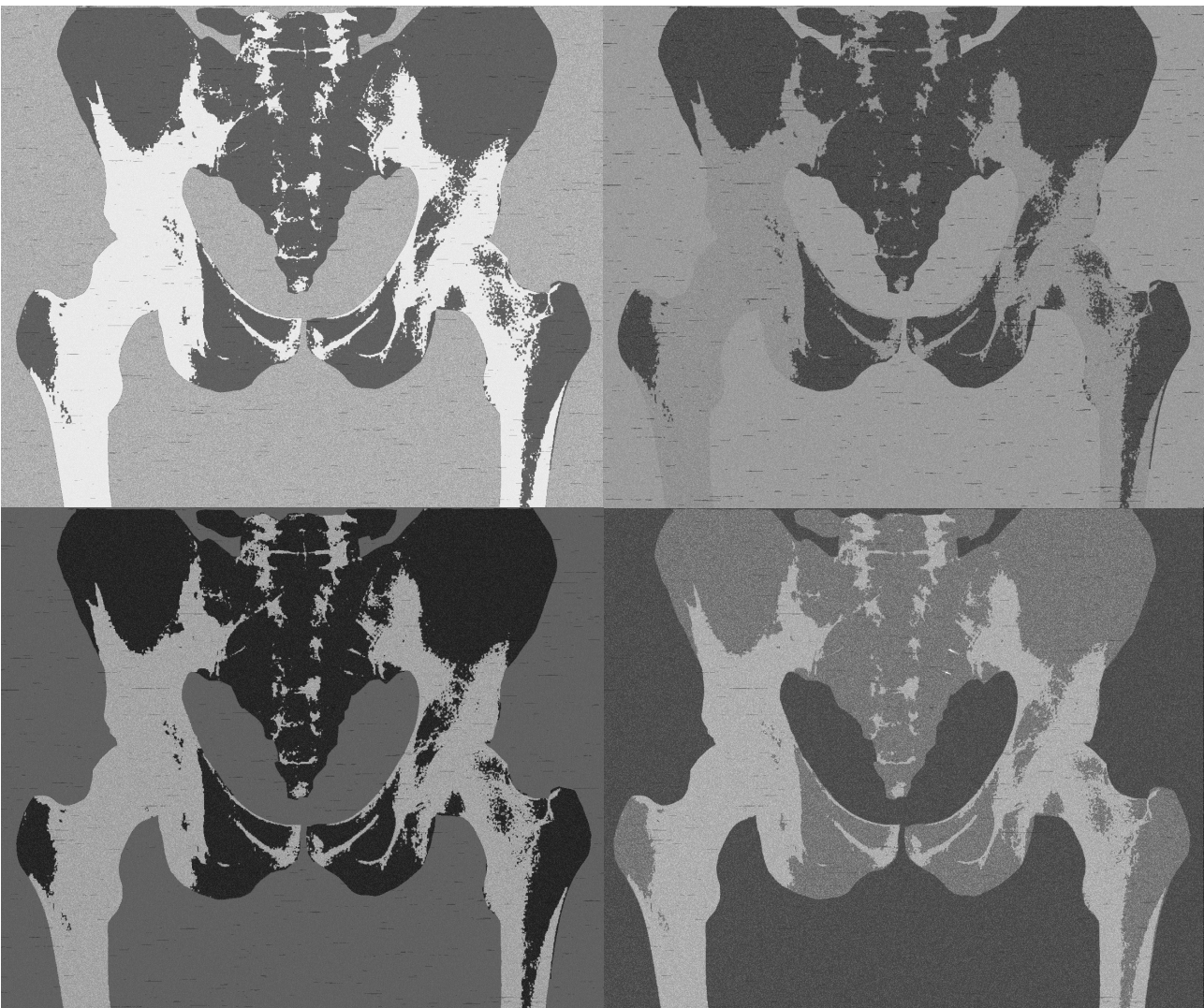

Abstract

Objective

To perform a literature review as basis for the update of the Assessment in SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) treatment recommendations with biologics in AS.

Methods

A literature search of all publications found in MedLine, Embase and Cochrane database between 2005 and 2009 and in the EULAR/ACR meetings between 2007 and 2009 was performed. The research evidence and strength of recommendation (SOR) for biologics were provided.

Results

Out of 247 reports on AS treatment with biologics, 98 contained efficacy data and 25 had complete data for analysis. The treatment effect sizes (95% CI) for anti-TNF versus placebo varied between 0.34 (0.08, 0.6) and 1.5 (0.45, 2.5) for BASDAI and 0.33 (0.07, 0.59) and 2.5 (1.3, 3.7) for BASFI. The calculation of the numbers needed to treat all the different outcomes varied between 2.3 and 3.0 patients for all ASAS outcomes and between 2.7 and 6.5 patients for ASAS partial remission. Data on biologics other than anti-TNF and for TNF blockers on juvenile SpA were limited. The incidence rates of uveitis during anti-TNF treatment varied between 4.4/100 patient-years (pys) and 15.6/100 pys during placebo ($p<0.05$). The incidence rates of IBD flares were significantly less during infliximab treatment (0.2/100 pys). The rate of infections was higher in patients treated with anti-TNF as compared with placebo, but there was no difference in the incidence of serious infections for treatment with anti-TNF versus placebo.

Conclusions

The overall evidence was very high for anti-TNF treatment (1b, SOR: A) with respect to efficacy and safety, while it was low for biologic treatment other than anti-TNF (3, SOR: C).

Introduction

Treatment with anti-TNF has shown short- and long-term efficacy without major safety issues in clinical trials of patients with active AS. At the moment, four different anti-TNF agents are available and approved for the treatment of AS (infliximab, etanercept, adalimumab and golimumab).

In 2003, the Assessment in SpondyloArthritis international Society (ASAS) proposed recommendations for the use of anti-TNF agents in patients with AS, based on a Delphi questionnaire, published data, clinical expertise and a consensus meeting among experts [1, 2]. In 2006, the ASAS/European League Against Rheumatism (EULAR) management recommendations of AS were published.

These include guidance on non-pharmacological and pharmacological treatment including the use of TNF blockers. The recommendations for the use of anti-TNF agents and the ASAS/EULAR management recommendations are complimentary.

The recommendations for the use of anti-TNF agents were updated in 2006 [3], since it was felt that the research had rapidly evolved in this area after the first publication. In the first update, several aspects of treatment with anti-TNF agents, such as the initiation, use and withdrawal of anti-TNF treatment, based on data on the efficacy and safety of those agents were taken into account. In 2009 it was decided that a second update of both the ASAS/EULAR recommendations for the management of AS and the recommendations for the use of anti-TNF agents should be performed. Two systematic literature reviews were performed to search for the underlying evidence: one on biologics and one on non-pharmacological and pharmacological (excluding biologics) treatment.

The primary outcome of interest for this systematic literature review was the evidence on the long-term efficacy and safety of TNF blockers in AS. This includes information on a possible distinction between the different TNF blockers, information about switching between TNF blockers in case of inefficacy or safety concerns, efficacy and safety of other biologics than TNF blockers and the efficacy of biologics including TNF blockers in patients fulfilling the ASAS classification criteria for axial SpA but not yet the modified New York criteria for AS.

Methods

Included study designs

Randomized controlled trials (RCTs) were considered as the ideal study design for calculation of the intended analyses.

However, since a low number of RCTs was anticipated, all possible studies (quasi-randomized studies, non-randomized studies, case-control studies) as well as abstracts from the EULAR and ACR annual meetings for the years 2007-09 were included.

Systematic literature search

A systematic literature search for published articles was performed for the time period 1 January 2005 (which represents the date after the end of the last systematic literature review on this topic [4]) to 1 December 2009, using the PubMed, Embase and Cochrane databases with the assistance of an experienced librarian. Furthermore, a search of published abstracts in the online abstract libraries of the EULAR and the ACR annual meetings for the years 2007-09 for additional relevant but still unpublished studies was performed by hand. The terms that were used for each search were 'ankylosing spondylitis', 'spondyloarthritis', 'anti-TNF', 'biologics', 'infliximab', 'etanercept', 'adalimumab', 'anakinra', 'abatacept', 'rituximab' in all possible combinations of at least two of the terms and up to all terms together. The complete search strategies for the database searches are provided in supplementary appendix 1, available as supplementary data at Rheumatology Online.

Selection of studies

All reports (published papers and abstracts of meetings) had to deal with patients fulfilling the modified New York criteria for AS [5] or the ASAS classification criteria for SpA [6].

After collection, each title and abstract was examined for suitability in the review by excluding these studies that met the following exclusion criteria: duplicates of papers, incomplete data, reports that had longer follow-ups available in other papers than the ones found (in this case, the longer follow-up papers were included in the final analysis), case reports without follow-up information and publications or reports with 'wrong outcome' (e.g. listing AS or SpA as keywords but not reporting about these diseases in particular) (figure 1). The full papers that were excluded from the analyses are listed in supplementary appendix 2, available as supplementary data at Rheumatology Online.

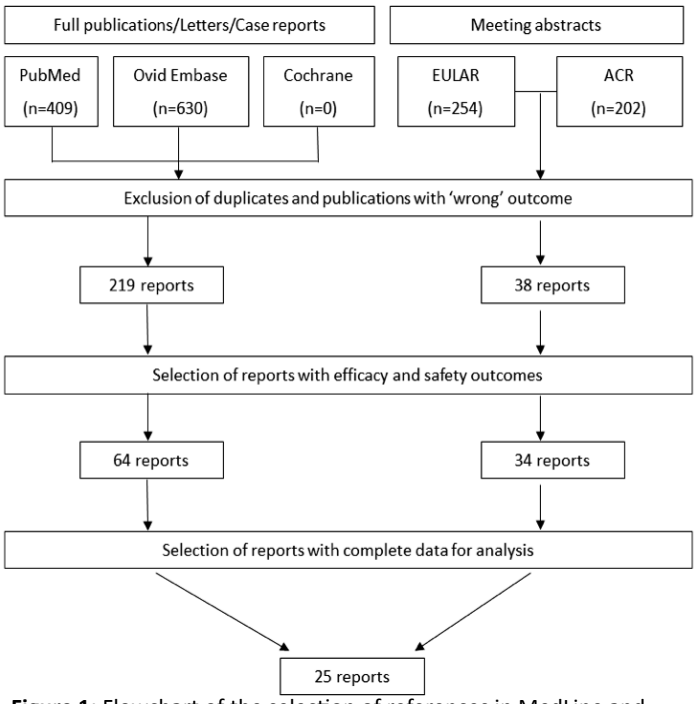

Figure 1: Flowchart of the selection of references in MedLine and Embase database as well as in the abstract books of the EULAR and ACR meetings, which served as the basis for this literature search. During the process, duplicates of papers, incomplete data, reports with longer follow-ups available in other papers, case reports without follow-up information and publications or reports with 'wrong outcome' were excluded.

Data extraction, data analysis and quality appraisal

From the studies that could be included in the analysis, all relevant efficacy and safety data were extracted and entered into standard data extraction forms in a Microsoft Excel- file according to the key components of the PICO (Participants, Interventions, Comparisons and Outcomes) method (supplementary appendix 1, available as supplementary data at Rheumatology Online). Calculations were made for the effect sizes (ESs, mean change in score divided by the baseline SD) for treatment [treatment effect (TE), the mean change in the index group minus the mean change in the comparator group divided by a pooled baseline SD] and for the Guyatt's ES (mean change in the index group divided by the SD of the change in the placebo group) according to all reported measures: disease activity (BASDAI [7]), metrology (BASMI [8]) and function (BASFI [9], CRP, ESR), but also the number needed to treat (NNT) for response to treatment according to the ASAS definitions (ASAS response [10]). The latter is used for assessment of the efficacy of study drugs by using the ASAS group core set of criteria for symptomatic improvement in AS [10] and is measured by a 20 and 40% response according to the ASAS criteria [10] and an improvement in the '5 out of 6 criteria' [11]. ASAS 20 response is defined as an improvement of not <20% and an absolute improvement of at least 1U (on a scale of 0-10) in at least three of the following

four domains: patient's global assessment, pain, function (represented by the BASFI score) and inflammation [represented by the mean of the two morning stiffness-related BASDAI numeric rating scale (NRS) scores]. Furthermore, there must be an absence of deterioration, which is defined as worsening of not >20% and net worsening of not >1U (on a scale of 0-10), in the remaining domain. Similarly, ASAS 40 response is defined as an improvement of not <40% and an absolute improvement of at least 1U (on a scale of 0-10) in at least three of the four domains mentioned above, while there should be no worsening in any of the domains. To meet the '5 out of 6 criteria', a 20% improvement in any five of the following six domains is required: the four domains used for ASAS 20 plus the CRP value and spinal mobility (assessed by the BASMI score).
Since we decided to include not only RCT alone, but also other types of studies (see above) in this review, a greater heterogeneity of the results was expected for all analyses.
A further assessment was made for each included study according to the Oxford Center for Evidence-based Medicine (CEBM) level of evidence, which gives studies a score for 'level of evidence' (1a-5) and a score for 'grade of recommendation' (A-D [12]). Analysis of safety data and adverse events (AEs) was done in a descriptive way in summary tables.
The results were finally presented to the ASAS/EULAR expert committee during the process of the update of the ASAS/EULAR management recommendations of AS and the update of the recommendations for the start of TNF-blocking agents.

Results

Process of the literature review

Overall, 409 reports were identified in MedLine and 630 reports were identified in the Embase database, while no report was found in the Cochrane database.
The search of the abstract meetings revealed 254 reports at EULAR and 202 reports at the ACR meeting. After exclusion of duplicates, 257 reports remained for validation, 64 reports were found to be dealing with efficacy and/or safety outcomes of patients and finally, 25 papers were found to have useful data for analysis (figure 1).

Efficacy

Calculation of ESs for treatment outcomes

The comparison between anti-TNF treatment versus placebo showed superior outcome for the treatment effect in favour of the anti-TNF treatment [13-21]. For the evaluation of the BASDAI, the ES (95% CI) varied between studies from 0.34 (0.08, 0.6) to 1.5 (0.45, 2.5) (table 1).
For evaluation of the BASFI, the ES (95% CI) varied between 0.07 (-0.21, 0.34) and 2.5 (1.3, 3.7), whereas for evaluation of the BASMI, the ES (95% CI) was only available for golimumab [0.08 (-0.20, 0.31)] (table 1).
Furthermore, data for different other outcomes such as occiput-to-wall measurements, chest expansion, physician's global and patient's global were only available in some of the studies [18, 20]. The treatment effect for patient's global assessment was 0.53 (0.17, 0.89), for physician's global assessment 1.3 (0.67, 1.9), for chest expansion zero (-0.35, 0.35), for occiput-to-wall it varied between -0.22 (-0.52, 0.09) and 0.01 (0.34, 0.37) and for modified Schober's test between 0.06 (-0.29, 0.42) and 0.28 (-0.03, 0.58).
The treatment effect for continuous versus on-demand anti-TNF treatment could only be calculated for infliximab, with an ES (95% CI) of 0.76 (0.44, 1.1) for BASDAI and 0.74 (0.42, 1.1) for BASFI, 0.53 (0.22, 0.84) for patient's global assessment, 0.03 (-0.28, 0.34) for the physical component of the short form 36 (SF-36) questionnaire and 0.19 (-0.12, 0.5) for the

mental component of SF-36.
The Guyatt's ES could only be calculated for golimumab in AS [19] and infliximab in non-radiographic SpA [21].

Calculation of numbers needed to treat

The calculation of the NNT for achieving all different treatment outcomes revealed only minor variations between the TNF blockers but superiority as compared with placebo [14, 18-26], with NNTs of 2.3-2.7 for ASAS 20, 2.9-3.7 for ASAS 40, 2.4-2.8 for ASAS 5/6, 2.5 for BASDAI 50 and 4.7-5.9 for ASAS partial remission.
Similar NNTs were found for patients with nonradiographic axial SpA, with 2.3 for ASAS 20, 1.6-2.4 for ASAS 40, 3.2 for ASAS 5/6 and 2.3-2.7 with ASAS partial remission (table 2).
In the comparison of continuous versus on-demand treatment with TNF blockers, the NNTs for ASAS 20 response were 4.2 versus 9.1 patients, for ASAS 40 response 6.7 versus 8.3 patients and for ASAS partial remission 5.9 versus 20.0 patients, respectively. For the differentiation between patients with versus without total spinal ankylosis, the NNTs varied between 2.4 for ASAS partial remission and 9.1 for ASAS 5/6 (table 3).

Efficacy of TNF blockers on extraspinal manifestations of the disease

One study from patients diagnosed as SpA according to the Amor criteria [27] provided data on the efficacy of TNF blockers in peripheral manifestations of the disease.
Patients with refractory disabling heel enthesitis were treated with etanercept or placebo. Patient's global assessment, heel pain and WOMAC improved significantly in the etanercept group as compared with placebo, already after 2 weeks of treatment.

Treatment with biologics other than TNF blockers

Overall, only small studies on biologics other than TNF blockers were available, and all of these studies included patients with advanced disease [28-32]. None of the studies was placebo-controlled. The compounds used were rituximab, anakinra or abatacept. All of the compounds showed only minor improvement in disease-related indices, and because there are no control groups, the level of improvement is difficult to interpret.
For rituximab in anti-TNF naïve patients [28], there were significant within-group improvements in BASDAI (p=0.047), pain as reported by the patient (p=0.021) and improvement in CRP (p=0.017). Further data published in the full paper of this abstract in 2010 showed a good improvement of all assessed parameters (50% in BASDAI50, 40% in ASAS 40) as compared with a poor response in those patients who had failed TNF blocker therapy before rituximab treatment (10% in ASAS40, none in BASDAI 50). For anakinra [31], the rate of patients showing sufficient ASAS response was reported as 25% for ASAS 20 and 20% for ASAS 40, while BASDAI improved from 5.8 to 4.6 and there was no change in CRP, as compared with baseline. The data of this study were included in abstract form in the first version of the recommendations [4], whereas the full paper is now available for the current report. For abatacept, there was only minor response of single patients [30].

TNF blockers in juvenile SpA

Only one small study published in abstract form [33] including patients with juvenile SpA patients with established AS (n=5 patients) and undifferentiated SpA (n=19) treated with infliximab could be used for data analysis. In this study, the amount of active joints, tender entheses, pain, CRP and HAQ showed significant decrease after 1 year in all patients. The mean amount of active joints decreased from 4.7 (1.7) to 0, the mean amount of tender entheses from 11.9 (10.7) to 0, the mean CRP from 24.8 (10) to 1.3 (3.1), the pain (mean of NRS) from 7.2 (2.0) to 1.7 (2.7), while the mean score in the childhood HAQ did not show

changes in the patients who were initially treated with infliximab and remained on this treatment.

Level of evidence and strength of recommendations for treatment with biologics in AS

The overall research evidence for all TNF blockers is rated with 1b+ (table 4), including two studies with patients with non-radiographic axial SpA [18, 21], which showed similar outcomes as compared with studies of patients with established AS.

Furthermore, the research evidence for the use of infliximab on demand and for the use of etanercept in a dose of 1x25 mg/week in patients with low disease activity was also rated with 1b+. There are no data on dose adjustment for adalimumab at the current time point.

The strength of recommendation (SOR) for the use of all available TNF blockers in AS in the recommended dose is rated with A, with the exception of treatment with etanercept 1x25 mg/week, where the SOR is rated with B (table 4).

The research evidence for the treatment of patients with DMARDs concomitant to TNF blockers as well as switching between TNF blockers is 3+, while the SOR was rated with C. Although the analyses for switching between anti-TNF compounds have been based on patients treated with infliximab after failure of treatment with etanercept, it is expected that other combinations among other TNF blockers would reveal similar outcomes.

For treatment with biologics other than TNF blockers, the available data showed a research evidence of 3 for anakinra based on the same study as already included in the previous review; however, this result remains to be confirmed by further studies. Data for abatacept and rituximab are scarce and did not allow for any conclusions, while no data for tocilizumab were available within the period of analysis in this update. The SOR for the use of anakinra in AS was rated with C.

For the use of biologics in patients with juvenile onset of SpA, only data on infliximab were available. The research evidence was 3, which can be translated to SOR rated with C (table 4).

Incidence of concomitant extra-articular manifestations in AS during treatment with TNF blockers

TNF blockers showed beneficial effect on the treatment of extra-articular manifestations (EAMs) of AS as compared with treatment with placebo. Data were available for infliximab, etanercept and adalimumab, while data from studies with golimumab were not available at this time point.

Two main concomitant EAMs were recognized: anterior uveitis (AU) and IBDs.

As suggested in a meta-analysis for the treatment of AU, which included only patients with infliximab and etanercept (adalimumab data were not available at this time point), the incident rates during anti-TNF treatment were 4.4 (range 1.1-8.0) per 100 patient-years (pys) as compared with 15.6 (7.8-27.9)/100 pys during placebo treatment (all $p<0.05$) [34, 35]. In a more recent paper [35], the incidence of AU flares under open-label adalimumab treatment was 7.4/100 pys and statistically significantly lower than the incidence rate of AU during the previously performed placebo-controlled period of the same trial with 15.0 AU flares/100 pys ($p=0.001$).

Another follow-up study with patients treated open label with etanercept showed similar superiority of etanercept (13 AU flares/100 pys), as compared with the numbers known from the placebo-controlled period of the same trial [36]. Similar data were shown in a meta-analysis that was available in abstract form [37] (the full paper was published in 2010).

Table 1: Effect sizes (ES) for treatment effect and Guyatt´s ES with 95% confidence interval (95% CI) for BASDAI, BASFI and BASMI outcomes.

			BASDAI		BASFI		BASMI	
Study	**n patients (treatment / comparator)**	**Treatment duration**	**Treatment effect (95% CI)**	**Guyatt'S ES (95% CI)**	**Treatment effect (95% CI)**	**Guyatt'S ES (95% CI)**	**Treatment effect (95% CI)**	**Guyatt'S ES (95% CI)**
ETN 2x25mg vs. Placebo [15]	9 / 11	24 weeks	1.5 (0.45 – 2.5)	--	2.5 (1.3 – 3.7)	--	--	--
ADA 40mg vs. Placebo [18]	22 / 24	12 weeks	1.2 (0.57 – 1.8)	--	0.07 (-0.21 – 0.34)	--	--	--
GOL 50/100mg vs. Placebo [19]	278 / 78	24 weeks	0.34 (0.08 – 0.60)	1.3 (1.0 – 1.6)	0.33 (0.07 – 0.59)	0.95 (0.68 – 1.2)	0.08 (-0.20 – 0.31)	0.60 (0.34 – 0.86)
INF 5mg/kg cont. vs. on demand [20]	124 / 61	58 weeks	0.76 (0.44 – 1.1)	--	0.74 (0.42 – 1.1)	--	--	--
INF 5mg/kg on demand +/- MTX [20]	62 / 61	58 weeks	-0.15 (-0.50 – 0.21)	--	0.27 (-0.08 – 0.63)	--	--	--
ETN 2x25mg vs. 1x25mg [17]	20/21	6 months	-1.0 (-0.35 – 1.7)	--	--	--	--	--
INF 5mg/kg vs. Placebo [21]	20/20	16 weeks	--	1.41 (0.72 – 2.1	--	1.2 (0.53 – 1.87)	--	--

A value of <0,6 indicates a small, a value of <0,8 indicates a moderate, a value of ≥0,8 indicates a large change. INF = infliximab, ETN = etanercept, ADA = adalimumab, GOL = golimumab.

Table 2: Calculation of numbers needed to treat (NNT) for the comparison of treatment between TNF blockers and placebo.

Study	Intervention vs. Placebo	Duration of follow-up	n patients (treatment / placebo)	Calculated NNT for different treatment outcomes				
				ASAS 20	ASAS 40	ASAS 5/6	BASDAI 50	Part. Rem.
van der Heijde et al [14]	ADA 40mg	12 weeks	208/107	2.7	3.7	2.8	--	5.9
Haibel et al [18]	ADA 40mg (no sacroiliitis on X-rays)	12 weeks	22/24	2.3	2.4	--	--	2.7
Inman et al [19]	GOL 50/100mg	24 weeks	278/78	2.6	3.0	--	--	--
Barkham et al [21]	INF 5mg/kg	16 weeks	20/20	--	1.6	3.2	--	2.3
van der Heijde et al [22]	INF 5mg/kg	24 weeks	201/78	2.4	2.9	2.4	2.5	4.7

Part. Rem.: ASAS partial remission; INF: infliximab; ADA: adalimumab; GOL: golimumab.

A summary of the studies dealing with the occurrence of AU in patients with anti-TNF during the time period analysed in this update is shown in table 5.

For the incidence of IBD, other differences between the TNF blockers were found, with significantly lower incidence rates during treatment with infliximab, as compared with etanercept or adalimumab [38] (table 6).

Safety

AEs

The incidence of AEs between treatment with TNF blocker and placebo, between TNF blockers in different treatment doses or during treatment with TNF blockers with or without concomitant treatment with other compounds is shown in table 7. Overall, the incidence of AEs as reported in the present updated review is in line with those reported in the first version of the recommendations [4].

Infections

In a meta-analysis comparing the risk difference between TNF blockers and placebo [39], the incidence rate of non-serious infections was 84.5 (58.4)/100 pys in patients treated with TNF blockers during the randomized control phases of the trials (RCTs) and reduced to 64.4 (56.7)/ 100 pys during the open-label phases. The latter was similar to the incidence of non-serious infections registered in the placebo arm of the RCTs, with an incidence of 63.6 (63.0) non-serious infections/100 pys.

In contrast, the analysis of serious infections showed an incidence of 2.3 (4.0) under TNF blockers during the RCTs and of 1.4 (2.8) during the open-label phases, as compared with an incidence of 1.4 (2.83) serious infections under placebo. An overview on the available data of the relative risk for infections in patients with AS is shown in table 7.

Table 3: Calculation of numbers needed to treat (NNT) for the comparison of treatment between TNF blockers and other comparators or between different groups with the same treatment.

Study	Intervention	Duration of follow-up	n patients (treatment / comparator)	Calculated NNT for different treatment outcomes				
				ASAS 20	ASAS 40	ASAS 5/6	BASDAI 50%	Part. Rem.
Breban [20]	INF 5mg/kg, continuous use	58 weeks	124/123	4.2	6.7	--	--	5.9
	INF 5mg/kg on demand use, addition of MTX	58 weeks	61/62	9.1	8.3	--	--	20.0
van der Heijde et al [23]	ETN 1x50mg	12 weeks	206/201	2.7	3.9	2.3	2.5	3.9
van der Heijde et al [23]	ETN 2x25mg	12 weeks	201/206	2.9	4.8	2.3	2.6	6.5
Marzo-Ortega [24]	MTX+Plac vs. MTX+Inf	30 weeks	28/14	3.1	--	--	--	--
Pérez-Guijo [25]	INF 5mg/kg + MTX 7.5 mg/ week	30 weeks	9/10	1.5	--	--	--	3.0
Cheung [26]	INF 5mg/kg with vs. without spinal ankylosis	54 weeks	11/16	5.6	5.0	9.1	5.6	2.4

Part. Rem.: ASAS partial remission; INF = infliximab; ETN = etanercept.

Formation of antibodies against TNF blockers

Only a few studies were dealing with the issue of antibody formation during treatment with TNF blockers in AS. In one study with infliximab [40] - patients who discontinued and re-started TNF blockade in the same treatment regimen - immunogenicity had no influence on the response to re-treatment or on safety outcomes in the long-term follow-up. While antibody formation due to immunogenicity was not detected during and after treatment with etanercept [41], antibody formation correlated well with undetectable serum trough levels, with inefficacy and infusion or injection reactions in patients treated with infliximab [42] or adalimumab [43] in two small studies.

Table 4: Research evidence for treatment with different biologic compounds and dosages in patients with AS and SpA for the years 2006 - 2010, compared to the last published version of the recommendations from the years 2001 - 2005 [4].

Intervention	Research Evidence		SOR (A–D)
	2005	2010	
INF 5mg/kg cont. *(only AS)*	1b+	1b+	A
INF 5mg/kg cont. *(non-radiographic SpA)*	NA		
INF 5mg/kg on dem.	NA		A
INF 5mg/kg on dem. + MTX	NA		A
ETN 1x50mg	NA	1b+	A
ETN 2x25mg	1b+		A
ETN 1x25mg	NA		B
ADA 1x40mg	3+ *(only AS)*	1b+ *(both AS and non-radiographic SpA)*	A
GOL 1x50mg/100mg	NA	1b+	A
Switch (INF to ETN)	NA	3+	C
Anakinra, Abatacept, Rituximab	3± *(anakinra only)*	3±	C
INF 5mg/kg in JuvSpA	--	3	C

+ = supportive, - = not supportive, ± = uncertain. SOR = strength of recommendations; NA = no data available.

Discussion

This report is a systematic literature review that was performed in order to obtain the detailed data for the second update of the ASAS/EULAR recommendations for the management of AS, with a special topic of interest being the treatment with biologics. After the first version of the recommendations published by ASAS in 2003 [2] and a first update in 2006 [3], a substantial number of new publications with long-term data on TNF blockers and reports on other biologics made this second update necessary.

On the basis of the published data on efficacy and safety, the research evidence is determined and the SOR is provided.

More data on all TNF blockers approved for the treatment of AS were available for the time January 2005-December 2009, as compared with the time before 2005, where the first version and the first update of the recommendations were available. Overall, all anti-TNF blockers proved to be efficacious in AS and SpA with a high level of research evidence (1b+).

Table 5: Effect of TNF blockers on anterior uveitis (AU) and incidence of anterior uveitis during treatment with TNF blockers as compared to treatment with placebo in patients with AS.

Trial	Type of trial	INF (n/100py)	ETN (n/100py)	ADA (n/100py)	Placebo (n/100py)
Braun J et al [35]	Meta-analysis n=717	4.4 (1.1-8) p=0.005 vs Plac.	7.9 (5.5-11.1) p=0.05 vs Plac.	--	15.6 (7.8-27.9) p=0.01 vs. INF+ETN
Rudwaleit et al [36]	Open-label ADA n=1250	--	--	7.4 p=0.001	15.0
Davis [37]	Double-blind + Open label ETN n=406	--	13	--	22
Sieper J et al [38]	Meta-analysis Double-blind ETN n=508	--	8.6 (4.5-14.2) p=0.031 vs. Plac.	--	19.3 (11.0-29.8) n=249
	Meta-analysis ETN vs. SSZ n=379	--	10.7 (5.5-17.4) p=0.486 vs. SSZ	--	SSZ: 14.7 (6.5-26.5) n=187
	Meta-analysis Double-blind + Open label ETN n=1074	--	12.0 (10-14.1)	--	--

Numbers indicate the occurence of AU per 100pys under treatment with either TNF blockers or placebo. ETN = etanercept; ADA = adalimumab.

Table 6: Incidence of acute inflammatory bowel disease (IBD) in AS patients treated with anti-TNF. P values were p<0.001 for infliximab versus. etanercept, 0.02 for infliximab versus. adalimumab and 1.0 for etanercept versus. adalimumab [39].

Treatment	Incidence of IBD / 100 patient years	Total number of treated patients	Numbers of IBD cases
Placebo	1.3	434	2
Infliximab	0.2	366	1
Etanercept	2.3	419	14
Adalimumab	2.3	295	3

Table 7: Calculation of relative risk (RR) and 95% confidence intervals (95% CI) for infections in patients with AS, as pooled relative risk for the placebo-controlled trials and for trials with comparators other than placebo.

Type of study	Adverse event	Study	RR (95% CI)
Studies comparing TNF treatment with placebo	Serious infections	Meta-analysis of anti-TNF vs. placebo treatment [40]	Risk difference: 0.4% (95% CI -8% to 1.6%)
Studies comparing TNF treatment with other comparators than placebo	All adverse events (for comparison)	Etanercept 1x50mg vs. 2x25mg [23]	0.84 (0.39 - 1.81)
	Infusion reactions	Infliximab continuous vs. on demand [20]	2.23 (1.00 - 4.94)
		Infliximab on demand, without vs. with MTX [20]	3.04 (0.64 - 14.52)

In comparison, the data of the last recommendations were only based on patients with established disease, proposing a research evidence level of 1b+ for continuous infliximab (5 mg/kg/6 weeks) and for etanercept (2-25 mg/week) but a research evidence level of 3+ for adalimumab (40 mg/2 weeks), while there were no data for the treatment with etanercept in the dose of 1-50 mg/week or for golimumab. In this update, also a research level evidence of 1+ can be given to adalimumab and golimumab in the approved doses.

The SOR for the use of all available TNF blockers in AS in the dose recommended by the label of each compound is rated with A. However, the present calculations also support treatment with infliximab on demand and treatment with etanercept in the decreased dose of 1-25mg for patients with established AS who remain on low disease activity (research evidence 1b+). For the latter, the SOR is rated with B. There are no data on dose adjustment for adalimumab at the current time point.

In contrast to the previous version of the recommendations, data on the treatment with DMARDs concomitant to TNF blockers as well as switching between TNF blockers are now available. The calculated research evidence is 3+, while the SOR was rated with C. Although the analyses for switching between anti-TNF compounds have been based on patients treated with infliximab after failure of etanercept treatment, it is expected that other combinations among other TNF blockers would reveal similar outcomes.

Data from new biologic compounds other than TNF blockers were also available this time. However, only studies with anakinra provided information that could be used for calculations, showing a research evidence of 3 (SOR rated with C). Data for abatacept, rituximab and tocilizumab were scarce and did not allow for any conclusions.

For the use of biologics in patients with juvenile onset of SpA, only limited data were

available. There, infliximab showed research evidence on a level of 1b+, which can be translated to a SOR rated with A.
Finally, the available data indicate a beneficial effect of TNF blockers for the treatment of the two main EAMs in the same patients, AU and inflammatory bowel diseases, with only minor differences between the available compounds.
With respect to safety, the overall incidence of AEs was not different to what had been reported previously.
However, treatment with TNF blockers showed a somewhat higher infection rate as compared with placebo, although there was no difference between the treatments in the comparison for serious infections. Nevertheless, it seems that the overall incidence of infections during treatment with TNF blockers decreased with longer duration of the studies, which might be due to selection of patients who stay in the study. In the short-term follow-up studies with patients treated with biologics other than TNF blockers, no major safety issues were reported. Finally, the formation of antibodies against TNF blockers has been reported in some studies and has correlated with low serum levels of the compounds, mainly in studies with mAbs. Nevertheless, immunogenicity had no influence on the response to re-treatment or on safety outcomes in one small study. More data are necessary to determine the clinical relevance of the formation of anti-drug antibodies.
In conclusion, the analysis of all available literature data support the use of the currently available TNF blockers for the treatment of patients with advanced AS who are fulfilling the ASAS recommendations for such treatment.
Furthermore, data from first studies from patients with non-radiographic SpA show a similar response to TNF blockers. Overall, biologics other than TNF blockers cannot be recommended at the current time because of lack of sufficient evidence. DMARDs do not add to efficacy or safety as concomitant treatment with anti-TNF in patients with AS. TNF blockers show good evidence in patients with juvenile onset of SpA, but these data are based on a limited number of studies.

Supplementary data

Supplementary data are available at Rheumatology Online.

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