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BIOLOGICS FOR TREATING AXIAL SPONDYLOARTHRITIS

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ABSTRACT

Introduction: Spondyloarthritis (SpA) encompasses a heterogeneous group of diseases sharing genetic, immunological, clinical and imaging features. Axial spondyloarthritis (axSpA) refers to a subgroup characterised predominately by inflammation of the axial skeleton with subsequent symptoms of chronic (often inflammatory) back pain and sacroiliitis. There is a strong association with the major histocompatibility complex (MHC) class I allele human leukocyte antigen (HLA) B27. In the last decade, there has been significant progress in earlier detection of the disease and the molecular mechanisms involved in its pathogenesis. The subsequent introduction of anti-tumour necrosis factor (TNF) has revolutionised the treatment of patients with axSpA.

Areas covered: In this article, we review the current biologic therapies for axSpA, the emergence of biosimilars, predictors of response, primary and secondary failure and new biologics on the horizon.

Expert opinion: There have been significant advances in the treatment of axSpA. Beyond the clear efficacy of anti-TNF inhibition, IL-17 offers an alternative therapeutic target and there is promise from inhibition of the IL-17/IL-23 pathway and small molecules, such as Janus kinase (JAK) inhibitors. Biosimilars have offered greater affordability and choice within this increasingly growing field of therapeutics.

Keywords: *Spondyloarthritis, ankylosing spondylitis, biologics, anti-TNF, anti-IL17, biosimilars.*

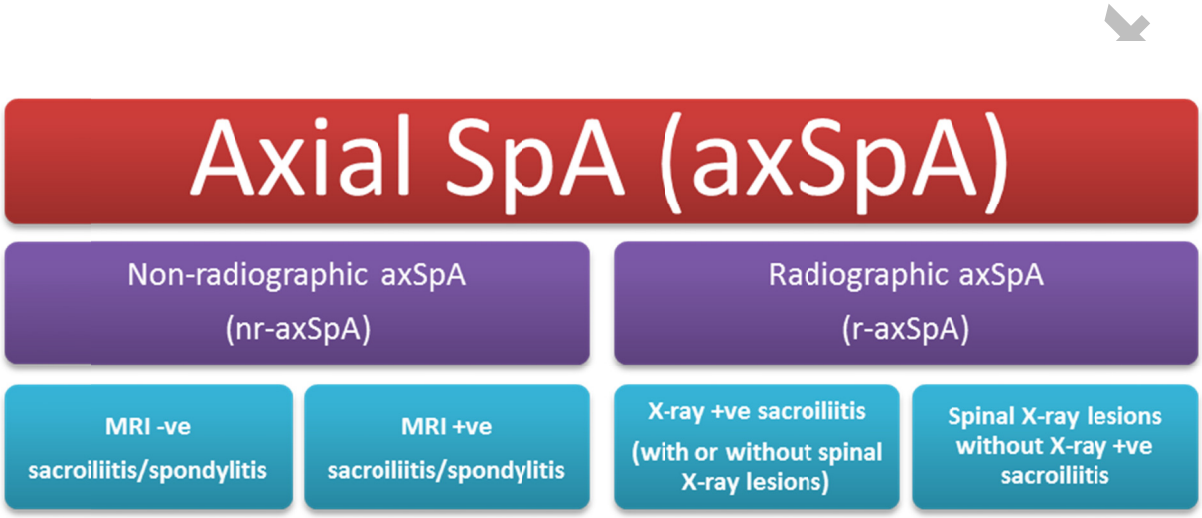
1. INTRODUCTION

Spondyloarthritis (SpA) encompasses a group of immune-mediated inflammatory diseases that classically include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel disease and a subgroup of juvenile idiopathic arthritis (JIA). Clinically, these conditions are characterised by axial inflammation, peripheral arthritis, enthesitis, dactylitis and extra-articular features such as psoriasis, uveitis and inflammatory bowel disease. They share similar pathogenic mechanisms and are strongly associated with the major histocompatibility complex (MHC) class I allele human leukocyte antigen (HLA) B27 (1). The disease typically affects young men and women in their second and third decades of life with a prevalence ranging from 0.2% in South-East Asia to 1.6% in Northern Arctic communities (2).

The Assessment of Spondyloarthritis International Society (ASAS) simplified the classification of SpA by dividing the group into axial(3) and peripheral SpA(4). Peripheral SpA (pSpA) refers to disease with predominantly peripheral features of enthesitis, arthritis or dactylitis; and axial SpA (axSpA) encompasses patients with inflammation of the axial skeleton. Axial SpA includes patients with ankylosing spondylitis (AS) with established sacroiliitis on X-ray. It also includes a further subgroup called non radiographic axial SpA (nr-axSpA). This subgroup was created owing to the recognition of early axial disease on MRI. Typically, these patients have symptoms of chronic (often inflammatory) back pain with evidence of (active/acute) sacroiliitis on MRI in the absence of definite X-ray changes; in order to fulfil classification criteria, nr-axSpA patients must also have at least one other SpA feature: this includes inflammatory back pain, arthritis, enthesitis of the heel, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to non-steroidal anti-inflammatories (NSAIDs), family history for SpA, HLA B27 or elevated CRP. HLA-B27 positive patients who have at least 2 additional SpA features can also fulfil ASAS classification criteria for axSpA, even in the absence of imaging features (clinical arm of the classification criteria). ASAS classification criteria are only applicable to patients with an onset of chronic back pain before the age of 45 years. Of note, the ASAS classification criteria are not meant to be used as diagnostic criteria; classification criteria are primarily intended to create well-defined homogeneous groups of patients with a classical disease picture. The conceptual model representing the entire spectrum of axSpA is presented in Figure 1.

In this article, we shall review the treatment algorithm for axSpA with a primary focus on the different biologic therapies available and the evidence for their use. We shall discuss predictors of response to biologics and causes of primary and secondary failure. Finally, we shall examine novel therapeutic targets and potential biologics on the horizon.

Figure 1. The spectrum of axial spondyloarthritis (axSpA). MRI positivity (active sacroiliitis/spondylitis based on the presence of typical bone marrow oedema lesions on MRI*) may fluctuate over time. Non-radiographic axSpA is not necessarily a pre-radiographic form of the disease, since many patients do not progress to radiographic axSpA. Spinal X-ray lesions are syndesmophytes, bridging of the vertebral bodies and ankylosis of the facet joints. *Currently, only MRI positivity of the sacroiliac joints is included as one of the items of the ASAS classification criteria for axSpA.



2. MANAGEMENT OF AXIAL SPONDYLOARTHRITIS

Prior to the introduction of biologic therapies, treatment of axSpA was limited to non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. Both have demonstrated efficacy in improving symptoms of inflammatory back pain and NSAIDs can also be effective in reducing the level of acute phase reactants such as C-reactive protein (CRP) (5). Unfortunately, axial and entheseal manifestations of SpA do not respond well to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs).

There is some controversy regarding NSAIDs and radiographic progression of axial disease. Wanders *et al* showed that when taken continuously as a daily dose over 2 years, Celecoxib was able to reduce radiographic progression of spinal disease compared with an on-demand treatment schedule (6). However, results from a more recent randomised multicentre trial (ENRADAS) in AS patients showed that continuous Diclofenac over 2 years did not reduce radiographic progression compared to on-demand treatment (7). A sub analysis of the Wanders study showed that patients with elevated acute phase reactants seemed to benefit most from continuous treatment with Celecoxib (8). Another study in patients with AS over 2 years, demonstrated slowing of new bone formation in the spine of patients with a high NSAID intake compared with patients with low NSAID intake. This protective effect was nearly exclusively seen in patients with elevated CRP levels and the presence of syndesmophytes at baseline (9).

Seminal studies for the use of biologics in axSpA are listed in Table 1. There are currently five licensed anti-TNF drugs for the indication of axSpA: Adalimumab, Certolizumab, Etanercept, Golimumab and Infliximab (in alphabetical order). These therapies can be used as monotherapy, without the need to combine them with csDMARDs. All, except Infliximab, have European Medicines Agency (EMA) approval for both radiographic and non-radiographic axSpA. Biosimilars of Infliximab, Etanercept and Adalimumab have also been approved by the EMA. The IL-17 inhibitor, Secukinumab, has also been approved by the EMA but only for axSpA patients with radiographic sacroiliitis. The European label for nr-axSpA is restricted to patients with objective signs of inflammation by elevated CRP and/or MRI inflammation. The US Food and Drug Administration (FDA) has approved Adalimumab, Etanercept, Certolizumab, Golimumab and Infliximab for the treatment of AS. However, in October 2013, the FDA rejected Adalimumab and Certolizumab for treatment of nr-axSpA. Among other reasons, the FDA's primary concern was regarding the specificity of the ASAS axSpA classification criteria when erroneously used for diagnostic purposes. In the UK, Infliximab was licensed for the treatment of AS in 2008. Subsequently, the other four TNF inhibitors were introduced for the treatment of AS. In December 2016, the IL-17 inhibitor, Secukinumab, was approved by the National Institute for Clinical Excellence (NICE) for treatment of AS. Adalimumab, Etanercept, Certolizumab and Golimumab (health technology appraisal for Golimumab published in January 2018) are all licensed for the treatment of nr-axSpA.

The safety of anti-TNF therapies in axSpA is comparable to other inflammatory joint diseases such as rheumatoid arthritis (RA). There is little evidence to suggest that safety issues differ hugely with different disease groups. More recent trials have not suggested any new or unkown safety signals for anti-TNF therapies (10).

2.1 Criteria for commencing biologic therapy

The ASAS-EULAR (2016 update) recommend commencing anti-TNF therapy in those with high disease activity defined by either a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 or an Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1 after two different NSAIDs for at least 4 weeks in total (11). The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommend anti-TNF drugs in patients with AS when activity persists despite NSAID treatment. No particular anti-TNF is preferred except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom anti-TNF monoclonal

antibodies should be used. In patients with active nr-axSpA despite treatment, conditional recommendations have been made for treatment with anti-TNF (12). The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines(13) and NICE guidelines (14) define high disease activity as a BASDAI and spinal pain visual analogue scale (VAS) score ≥4. According to the BSR, patients need to have failed two NSAIDs for at least two weeks each, unless contraindicated, and the BASDAI should be measured on two occasions at least 4 weeks apart.

2.2 Currently approved biologic therapies, including biosimilars

2.2.1 Adalimumab

Adalimumab is a fully human monoclonal antibody that binds with high affinity to TNF. The ATLAS trial demonstrated clear efficacy of Adalimumab in active AS over the 24-week study period. In this study 58.2% patients achieved a 20% Assessment of Ankylosing Spondylitis (ASAS20) improvement in the adalimumab group compared to 20.6% in the placebo group by week 12 (15). The use of Adalimumab in nr-axSpA was demonstrated by the ABILITY-1 study. In this study, ASAS40 response rates in the adalimumab treated group were 36% compared to 15% in the placebo group at week 12 (16). The long-term efficacy of adalimumab has been demonstrated in a 5 year follow-up study in patients with AS. In this study 70% of patients achieved ASAS40 (17).

2.2.2 Certolizumab

Certolizumab is a PEGylated Fc-free anti-TNF. A phase 3 double-blind, randomized study, evaluated the efficacy and safety of Certolizumab in patients with axSpA, including patients with AS and nr-axSpA. At week 12, ASAS20 response rates were significantly higher in the Certolizumab groups compared to placebo (57.7% (200mg) and 63.6% (400mg) vs 38.3% (placebo), $p \leq 0.004$). At week 24, patients in the certolizumab group showed significant differences in BASDAI, ASDAS, Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) scores. The results of this trial demonstrated that certolizumab led to rapid improvements in clinical signs and symptoms in axSpA (18). The clinical efficacy of Certolizumab in axSpA has been demonstrated at 4-year follow-up in patients with axSpA including AS and nr-axSpA (19). Sustained efficacy at the MRI level has been shown in a recently published 95-week study (20).

2.2.3 Etanercept

Etanercept is a recombinant TNF receptor p75 Fc fusion protein that acts competitively to inhibit cell surface receptor binding of TNF. Its safety and sustained clinical response in AS was studied in 277 patients who had participated in a previous randomised, double blind, placebo controlled 24 week trial that continued in an open label extension study for a total of 2 years. In the Etanercept group, 74% achieved an ASAS20 response after 96 weeks (21). Its efficacy in nr-axSpA was initially demonstrated in the ESTHER trial, where 50% of the patients (n=36) achieved remission in the etanercept group compared with 19% in the sulfasalazine group at week 48 (22). The long-term efficacy and safety of etanercept was demonstrated in a 7-year follow-up study of patients with AS, where 31% of patients were in ASAS partial remission, and 44% had ASDAS inactive disease (23). The EMBARK study was the pivotal study resulting in the market authorisation of Etanercept in nr-axSpA(24). This study showed rapid, significant improvement in symptomatic disease activity, function, and systemic and skeletal inflammation over 12 weeks. Clinical and functional improvement was sustained over 24 weeks.

2.2.4 Infliximab

Infliximab is a monoclonal chimeric human anti-TNF antibody that binds with high affinity to TNF. The efficacy of Infliximab was demonstrated in the ASSERT trial; a multicentre, randomised study, where 61.2% of AS patients in the Infliximab group were ASAS20 responders compared with 19.2% of patients in the placebo group (25). Persistent clinical efficacy and safety of infliximab was demonstrated after 8 years of follow-up in patients with active AS treated with Infliximab, where 24% of the patients were in partial remission (n=8) and 64% (n=21) had low disease activity (BASDAI <3) (26).

2.2.5 Golimumab

Golimumab is a humanised monoclonal antibody to TNF. In the GO-RAISE study, Golimumab was proven to be effective and well tolerated in a large cohort of patients with AS. At 14 weeks, about 60% achieved ASAS20 response in the golimumab treated patients compared to 21.8% in the placebo group (27). Golimumab has also been shown to be effective in nr-axSpA in the GO-AHEAD 16-week study, where the primary endpoint (ASAS20 at week 16) was achieved in 71.1% in the golimumab group versus 40.0% in the placebo group(28).

2.2.6 Secukinumab

Secukinumab is a monoclonal antibody of the IgG1/kappa isotype that targets interleukin-17. It has recently been licensed for treatment of AS in patients who have failed NSAIDs or anti-TNF. The MEASURE trials demonstrated safety and efficacy of Secukinumab in patients who were anti-TNF naive and those who had previously failed anti-TNF. In MEASURE 1 (371 patients), the ASAS20 response rates at week 16 were 61%, 60% and 29% for subcutaneous Secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($p<0.001$). In MEASURE 2 (219 patients), the ASAS20 response rates were 61%, 41%, and 28% for subcutaneous Secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($p<0.001$ for the 150-mg dose and $p=0.10$ for the 75-mg dose). There were also statistically significant improvements in the BASDAI 50 (the proportion of patients achieving a 50% improvement in BASDAI score) and in the change from baseline BASFI scores in the Secukinumab arms of the trials compared with placebo(29). An efficacy and safety RCT of Secukinumab in patients with nr-axSpA is ongoing (NCT02696031).

Table 1. Seminal studies for the use of biologics in axSpA

Outcome	Drug	Study	N patients	Time point (weeks)	Response to treatment (%)	Response to placebo (%)	NNT
ASAS-20	Adalimumab	ATLAS(30)	315	12	58.2	20.6	2.7
	Certolizumab (200mg)	RAPID-axSpA(18)	122	24	67.7	33.3	2.9
	Etanercept	Davis et al(31)	277	24	57	22	2.9
	Infliximab	ASSERT(32)	279	24	61.2	19.2	2.4
	Golimumab	GO-RAISE(33)	216	14	58.2	20.6	2.7
	Secukinumab (150mg)	MEASURE 1(29)	371	16	61	29	3.1
ASAS-40	Adalimumab	ATLAS(30)	315	12	39.4	13.1	3.8
	Certolizumab (200mg)	RAPID-axSpA(18)	122	24	47.7	15.8	3.1
	Etanercept	SPINE(34)	82	12	44.7	25.6	5.2
	Infliximab	ASSERT(32)	279	24	47	12	2.9
	Golimumab	GO RAISE(33)	24	54.3	15.4	15.4	2.6
	Secukinumab (150mg)	MEASURE 1(29)	371	16	43	13	3.3

Outcome	Drug	Study	N patient	Time point	Response to treatment	Response to placebo	NNT
ASAS-20	Adalimumab	ABILITY-1(16)	185	12	51.6	30.9	4.8
	Certolizumab	RADID-axSPA(18)	96	24	65.2	24.0	2.4
	Etanercept	EMBARK(35)	215	12	52.4	36.1	6.1
	Infliximab	-	-	-	-	-	-
	Golimumab	GO-AHEAD(36)	198	16	71.1	40.0	3.2
	Secukinumab	-	-	-	-	-	-
ASAS-40	Adalimumab	ABILITY-1(16)	185	12	36.3	14.9	4.7
	Certolizumab	RADID-axSPA(18)	96	24	56.5	14.0	2.7
	Etanercept	EMBARK(35)	215	12	33.3	14.8	5.4
	Infliximab	-	-	-	-	-	-
	Golimumab	GO-AHEAD(36)	198	16	56.7	23.0	3.0
	Secukinumab	-	-	-	-	-	-

2.2.7 Biosimilars

Biologics have revolutionized the treatment of axSpA. However, these drugs are expensive resulting in wide inequalities in their use. The emergence of biosimilars offers the promise of substantial savings relative to the reference medicinal product (RMP) enabling more patients to access biologic therapy. A biosimilar is defined by the World Health Organisation (WHO) as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product(37). It has been estimated that Germany, France and the UK each stand to save between €2.3 billion and €11.7 billion between 2007 and 2020 in response to the introduction of biosimilars (38).

Biosimilars of four RMPs, Adalimumab, Etanercept, Infliximab and Rituximab, have now been approved by the European Medicines Agency (EMA) for rheumatologic indications and those for which the bio-originator no longer is protected by patent, have been marketed. CTP-13, otherwise known as Remsima/Inflectra, was the first biosimilar approved by the EMA in September 2013. In January 2016, the EMA approved the first Etanercept biosimilar, SB4, otherwise known as Benepali. A further infliximab biosimilar, SB2/Flixabi, was approved in May 2016. In March 2017, the EMA approved the first Adalimumab biosimilar, SB5, otherwise known as Amgevita/Solymbic. The approval dates just mentioned represent the date of issue of a marketing authorisation valid throughout the European Union (EU). Currently, there are 700 biosimilar products in preclinical and clinical trials. Table 2 summarises the biosimilar studies to date (with relevance for the axSpA indication).

In 2015, the BSR published a position statement(39) on the use of biosimilars in practice. Notably, it was recommended that biosimilars should be prescribed by brand name rather than by non-proprietary name. This recommendation was in line with existing recommendations by the Medicines and Healthcare Products Regulatory Agency (MHRA) to avoid automatic or accidental substitution of a biosimilar product when the drug is issued by a pharmacist. The BSR have reiterated that clinical effectiveness and patient safety should be the overriding principles for prescribing any biologic agent and that prescribing should be on a case by case basis, based on clinical reasons and not solely as a measure to save money.

Table 2. Biosimilar studies (with relevance for the axSpA indication) demonstrating safety and efficacy in rheumatic diseases

Originator/Biosimilar	Study design	Indication(s)	No of patients	Type of switch	Follow-up post switch	Reference(study name)
Infliximab/CT-P13	DB RCT multi-centre	Crohn's, UC, SpA, RA, PsA, Psoriasis	408	One way bo→bs	52 weeks	Jorgensen et al, 2017 (NOR-SWITCH)(40)
Infliximab/CT-P13	OL extension of DB RCT	RA	302	One way bo→bs	48 weeks	Yoo D.H et al, 2016 (PLANETRA)(41)
Infliximab/CT-P13	OL extension of DB RCT	AS	174	One way bo→bs	48 weeks	Park W, et al 2015 (PLANETAS)(42)
Infliximab/CT-P13	Observational registry	RA, axial SpA, PsA, other polyarthritis	96	One way bo→bs	2-4 months	Glintborg B. et al, 2016 (43)
Infliximab/CT-P13	Observational single center study	RA, SpA, PsA, JIA, chronic reactive arthritis	39	One way bo→bs	variable	Nikiphorou E et al, 2015 (44)
Infliximab/SB2	DB RCT	RA	396	One way bo→bs	24 weeks	Smolen J. S. et al, 2016 (45)
Infliximab/SB2	DB RCT	RA	584	No switch Inflix v SB2	30 weeks	Choe et al, 2015(45)
Infliximab/innovator biosimilar	Observational Multi-centre	SpA/PsA Undifferentiated SpA	41	One way bo→bs	6 months	Benucci et al, 2017(46)
Etanercept/SB4	OL extension of DB RCT	RA	245	One way bo→bs	48 weeks	Emery P et al, 2017 (47)
Etanercept/SB4	SB crossover	-	138	One way bo→bs bs→bo	20 days	Lee Y. et al, 2016 (48)
Etanercept/GP2015	Two way crossover	-	54	One way bo→bs bs→bo	28 days	Von Richter et al, 2017 (49)
Etanercept/ABP 501	DB RCT	RA	494	One way bo→bs	24 weeks	Cohen et al, 2017(50)
Adalimumab/SB5	DB RCT	RA	508	One way bo→bs	28 weeks	WeinblattM. et al EULAR 2016 abstract FRI0161(51)

OL open-label; DB double-blind; SB single-blind; RCT randomised controlled trial; RA rheumatoid arthritis; Bo biologic originator; bs biosimilar, AS ankylosing spondylitis; SpA spondyloarthritis; PsA psoriatic arthritis JIA juvenile idiopathic arthritis; UC Ulcerative Colitis

3. Predictors of response to biologic therapy

The biologics registries have shown that factors associated with clinical response include raised inflammatory markers, higher ASDAS score, lower BASFI, and younger age at baseline (52–54). According to the Swedish register, male gender and presence of peripheral arthritis were also baseline predictors of continuation of anti-TNF therapy (55). Similar findings have also been reported in a large cohort of AS patients treated with Adalimumab. In this study HLA-B27 positivity and anti-TNF naivety were associated with better response to Adalimumab (BASDAI50, ASAS40) (56). Shorter disease duration (57) and active inflammatory lesions on MRI have also been shown to predict response to TNF therapy (58). The use of corticosteroids has been associated with a poor response to Infliximab in a small retrospective study of 70 patients with AS treated with Infliximab over a five-year period. In this study 71.4% patients responded within the first 6 months of treatment (59).

Pederson et al (60) investigated the demographic, smoking status, presence of HLA B27, NSAID use and baseline CRP in 480 patients with AS commenced on anti-TNF therapy. They also assessed MRI at baseline, 3-6 months and annually. They found that the strongest predictor of treatment survival was normalised CRP or low disease activity within the first year of anti-TNF therapy. Sustained remission was more likely in patients achieving normal CRP with definite SIJ erosion and absence of ankylosis. Current smoking was a negative factor associated with achieving sustained remission. Ciurea et al(61) assessed response rates to anti-TNF in nr-axSpA versus AS in a SWISS cohort of 152 women and 267 men who fulfilled ASAS axSpA classification criteria. Interestingly, they found that a significantly lower number of women with nr-axSpA achieved an ASAS40 response with anti-TNF compared with those

with AS. Responses were comparable in men with nr-axSpA and AS. More work is needed in this area to inform the optimisation of anti-TNF therapy in axSpA.

4. Switching biologics

Primary failure describes no response or inadequate efficacy in patients within 3-6 months of treatment with a biologic (62). A prospective multicentre longitudinal observational study using the Norwegian register, NOR-DMARD, assessed 514 patients with AS treated with anti-TNF (including Infliximab, Etanercept, and Adalimumab) of whom 77 switched to a second anti-TNF agent. The reason for switching was adverse events in 44 patients (57.1%) and insufficient response in 30 (38.9%) of the 77 switchers. The insufficient response group had been treated with the first TNF blocker for a median of 294 days, and the adverse event group has been treated with the first anti-TNF agent for a median of 171 days. For the first anti-TNF, the 2-year drug survival rate was 65%, and for the second anti-TNF it was 60%. The 3-month BASDAI 50 and ASAS 40 responses were achieved by 49% and 38% of the non-switchers, by 25% and 30% of switchers after the first TNF blocker, and by 28% and 31% after the second TNF agent. This study shows that switching to a second anti-TNF can be an effective approach in AS, with around one-third of patients showing a good clinical response and more than half of patients continuing the treatment for more than 2 years (63).

Of the 1436 AS patients from the Danish biologics register (DANBIO), 30% of patients switched to a second biologic and 10% switched to a third biologic. Switchers were more frequently women, had shorter disease duration, and higher BASDAI/BASFI and visual analogue scale (VAS) scores when they commenced their first anti-TNF agent. After 2 years of treatment, the response rates and drug survival were lower among switchers; however, 52% of them achieved response compared to 63% of non-switchers, therefore switching to another anti-TNF agent should be considered irrespective of the reason for discontinuation of the initial TNF blocker (64).

Of the 229 AS patients treated with biologics from the Finnish biologics register (ROB-FIN), 13 patients (7%) discontinued the first biologic due to lack of efficacy and 21 patients discontinued for unspecified reasons; 14 of these patients switched from Infliximab to Etanercept or Adalimumab. Adverse events occurred in 11% of the patients receiving their first biologic drug (25 of 229 patients). In this study, the dose of Infliximab was increased in more than a quarter of the patients in an attempt to improve response. There was also an extensive use of concomitant DMARDs such as Methotrexate and Sulfasalazine with biologic therapy, due to peripheral arthritis. The combination of DMARDs and Infliximab led to a rapid pain relief and improvement of patient's and physician's global assessments within six weeks, which was sustained at two years. A subgroup of AS patients with axial involvement only (n=46), had an ASAS20 response in 79%. The authors concluded that switching may be possible; however, the group of switchers in this study was small (13% of patients, n= 27) (65).

A retrospective analysis of 108 patients with severe AS on anti-TNF therapy showed that 15% were switched to a second anti-TNF agent, and two patients were switched to a third anti-TNF agent. Inefficacy was the most common reason for switching (67%), followed by adverse events (28%). At 69 months, 86% of patients who switched to a second anti-TNF drug were continuing treatment. Switching due to adverse events led to better response than switching due to inefficacy. Sustained benefit in AS patients treated with a second anti-TNF is similar to the efficacy seen following the initial anti-TNF therapy (66) (67)

In a 54-week, open-label, prospective study of patients with AS treated with Infliximab who failed to achieve or maintain an ASAS20 clinical response or had adverse events, were switched to Etanercept. At week 54, ASAS20, ASAS50, and ASAS70 response rates were 74%, 61%, and 39% respectively. These

figures suggest that switching to etanercept may be a good therapeutic option for patients who do not respond to Infliximab (68).

Some patients have a good initial response to biologic therapy which subsequently diminishes with time. This has been coined secondary failure and is defined as a loss of efficacy of a biologic agent after more than 6 months (62).

A longitudinal observational prospective study (69) evaluated the clinical response after switching from one anti-TNF agent to another in patients with AS and PsA over a 5-year period. A clinical response was seen in 75% of the patients who changed from Infliximab to Etanercept, and 57.1% who switched from Etanercept to Adalimumab. Patients who switched because of adverse events and lack or loss of efficacy, showed a similar clinical response; 70% and 61.5% respectively. In this study, 81.3% of patients who had switched from Infliximab to Etanercept continued the treatment, compared to only 57.1% of patients who had changed from Etanercept to Adalimumab maintained the treatment. Two of the three patients who stopped Adalimumab because of inadequate response had already failed the other two anti-TNF agents. This observation suggests that the failure of two TNF inhibitors predicts ineffectiveness to the third, which has been seen in previous data on RA patients. Patients with SpA with inadequate response or adverse events to one anti-TNF agent may be successfully treated with another, regardless of the reason for switching

Switching to a second anti-TNF agent was necessary in 24% of the AS patients, and 11% of AS received a third anti-TNF in an observational study (62). In this study, secondary failure was the main reason for switching to a second anti-TNF agent, followed by side effects and lack of efficacy, whereas the reasons for switching to a third anti-TNF were lack of efficacy, followed by side effects. As with the previous findings, patients with AS with loss of efficacy to the first anti-TNF who were switched to a second anti-TNF had an adequate response, suggesting that switching anti-TNF for secondary failure may be beneficial in this group of patients

In a cross-sectional study of 467 SpA patients drug survival and the reasons for switching anti-TNF therapy was studied (70). Of the 467 patients who started anti-TNF therapy, 28% switched to a second and 8% switched to a third drug. The mean drug survival did not differ among the courses of anti-TNF. In this study, the main reasons for switching were lack or loss of efficacy and adverse events in 40% and 30% of switchers respectively. Switchers were more frequently women and had higher disease activity parameters (BASDAI, ESR, and patient's visual analogue scale (VAS) for pain and for global state) at the time of the study than non-switchers

In a retrospective study of 113 patients with AS treated with anti-TNF including Adalimumab, Etanercept, Infliximab, long term response to biological therapy in AS in a real life clinical setting was investigated (71). This study looked at quantifying non-response and response to switching therapies. At week 12, 88% of the patients responded to their first anti-TNF. Primary non-response was seen in 13 patients (infliximab n=10, etanercept n=3), 7 of whom were switched to a second anti-TNF, with 6 showing a good clinic response, all to etanercept. A further 8 patients who initially responded to the initial biologic were also switched and the reasons were secondary failure to Infliximab (n=2), side effects (n=2) or patient choice (n=4). The primary and secondary non-response rates were less than 15%. Disease duration, HLA-B27 status or biologic drug used, did not show any differences in the response rates. The majority of non-responders had a good response when switched to another anti-TNF, supporting switching in this group of patients.

5. Radiographic progression

Despite its clear clinical efficacy, there is controversy regarding biologic therapy and disease modification in axSpA. Studies have shown clear inhibition of radiographic progression in patients with rheumatoid arthritis and psoriatic arthritis. However, these findings have not been replicated in studies of axSpA.

Radiographic progression in AS develops slowly and may be detectable only after a minimum of two years. Ethically, it is difficult to justify a placebo arm of two years when the clinical benefits of the treatment are well known and occur shortly after it is commenced. Thus, studies assessing radiographic progression in axSpA have either used observational data or compared the open-label extension phase of RCT of TNF inhibitors with historical cohorts not treated with TNF inhibitors. These historical cohorts include the Outcome in Ankylosing Spondylitis International Study (OASIS), the German Spondyloarthritis Inception Cohort (GESPIC) and the Herne Cohort (HC).

Baraliakos et al (72) analysed radiographs of patients from a multi-centre, double-blind, placebo controlled trial in Germany which assessed the safety and efficacy of Infliximab over two years(73). They compared radiographic images to the German AS Cohort (GESPIC) cohort who were treated conventionally; 82 patients were included in the study; 41 patients were randomly picked from the continuous treatment arm of the RCT and 41 patients were randomly selected from the GESPIC cohort. The mean modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) change in the Infliximab group was less than in conventionally treated patients but not significant so (p=0.085). Van der Heijde et al looked at radiographs at baseline and at week 96 from patients in the ASSERT trial and compared this to radiographs from patients from the OASIS cohort who were anti-TNF naive (74). In this study Infliximab treated patients did not show a statistically significant difference in inhibition of structural damage progression at year 2, as assessed using the mSASSS scoring system, when compared with radiographic data from the historical control OASIS cohort.

Van der Heijde assessed a total of 257 patients treated with Etanercept and compared radiographs with 175 unselected patients from the OASIS study. No significant difference was found in the mean change (SD) in mSASSS from baseline among patients who received Etanercept 0.91 (2.45) versus those from the OASIS group 0.95 (3.18) (75). The same group looked at radiographs from patients in the ATLAS study combined with a Canadian AS study (n=307). Radiographic progression from baseline to 2 years in the spine of these patients was compared to anti-TNF naive patients from the OASIS cohort (n=169). Again, mSASSS results were not significantly different between the Adalimumab cohort and the OASIS cohort after 2 years.

Baraliakos et al (76) assessed the rate of new bone formation after 8 years of Infliximab treatment in patients with AS. They compared the radiographic progression of 22 patients from the multi-centre DIKAS study (77). In DIKAS, all patients were treated with 5mg/kg Infliximab continuously every 6 weeks. They compared radiographic changes to those in the Herne Cohort. The selection of patients was made according to their availability of conventional radiographs of the cervical and lumbar spine at baseline and whether they continued anti-TNF for 8 years. Patients on Infliximab (n=22) and the Herne Cohort (n=34) did not differ in the baseline mSASSS status. Both showed significant radiographic progression after 8 years with a mean (SD) mSASSS of 20.2 (21.4) in DIKAS and 25.9 (17.8) in Herne Cohort. The mean mSASSS difference was similar in both groups between baseline and four years but radiographic progression between years 4 and 8 differed significantly between both treatment groups (p=0.01). The mean number of syndesmophytes, although similar at baseline differed significantly at 8 years (p=0.007). Adjustment for age, symptoms duration, HLA B27, BASDAI and Bath AS function index (BASFI) at baseline had no influence. This finding implies that delays in radiographic progression may occur but after a protracted period of time.

Haroon et al (78) designed a prospective study looking at all patients who satisfied the modified New York criteria for AS. The study found that those who received TNF inhibitors had a 50% reduction in

odds progression to those who had not been on anti-TNF (OR: 0.52; CI 0.30-0.88 p = 0.02). The total duration of treatment was inversely associated with progression compared to those who has not been on TNF inhibitors (OR: 0.52; CI 0.30-0.88; p=0.02). Patients who were on biologics for more than 50% of their disease duration had lower odds of progression (OR 0.2 95% CI: 0.04-0.92; p=0.04) compared to patients who were not. Patients who were not on anti-TNF for the greater part of their disease duration, had higher rates of mSASSS progression. In the patients who were on TNF-inhibitors, the rate of mSASSS progression increased with an increasing delay in starting treatment. This was the first study to show an association between the use of TNF inhibitors and progression of damage in AS. Haroon et al suggested that both the timing and duration of therapy could be important in rate of radiographic change. However, this study also raises methodological concerns, as it used a controversial definition of radiographic progression, the analyses did not take into account treatment changes and clinical changes between the 2 radiographic assessments and did not entirely account for time-varying variables in the statistical models (79).

A more recent observational cohort study by Maas et al looked at 176 AS patients receiving long-term TNF inhibitors and showed a reduction in spinal radiographic progression after more than 4 years of follow-up (80). These results may refer to a delayed effect of TNF inhibitors on radiographic progression. This finding supports the purported 'TNF brake hypothesis': That already-triggered repair processes can first lead to continuation of bone formation but long-term inhibition of inflammation by TNF inhibitors may result in a reduction of new bone formation overtime.

Finally, an even more recent study by Molnar et al (81), using 432 patients with AS in the Swiss Clinical Quality Management cohort with up to 10 years of follow-up and radiographic assessments every 2 years, demonstrated an association between TNF inhibitors' use and reduced risk of spinal structural damage, both in terms of mSASSS and new syndesmophyte formation. This effect was mediated by a decrease in disease activity (reduction in ASDAS/CRP).

In the RAPID-axSpA Certolizumab trial, after 4 years, 80.6% of patients with AS did not progress (<2 mSASSS points change from baseline) and the mean change was 0.98. The limited progression over 4 years observed in this study in patients with AS is consistent with MEASURE 1 Secukinumab trial, in which 79% of patients with AS treated with secukinumab did not progress (same definition: <2 mSASSS points change from baseline) over 4 years. However, none of these studies had a control group and therefore these findings cannot be used in isolation to confirm an effect of any of the drugs on structural damage (82)(83)

6. Biologic therapies on the horizon

The TOPAS trial gave promise to the inhibition of IL23 and IL12 with Ustekinumab in the treatment of ax-SpA. This was a 28-week, prospective, open-label study in patients with AS and prompted 3 subsequent phase 3 placebo controlled trials (NCT02437162, NCT02438787 and NCT02407223) assessing the safety and efficacy of Ustekinumanb in patients with both nr-axSpA and AS. However, this trial has been withdrawn as it has failed to meet any of its primary or secondary outcomes. A number of other biologics acting on the IL-17 and IL-23 axis are currently in clinical trials (Table 3).

Biologic drugs targeting other pathways, such as IL-1 and IL-6 blockers, B-cell depletion strategies and inhibition of T-cell costimulation, have been tested in uncontrolled or controlled trials in established AS. Trials on Anakinra (84),(85), Abatacept(86) , Rituximab (87),(88) and Tocilizumab (89) have shown no consistent efficacy.

Whilst Apremilast and Tofacitinib are not biologic therapies, they have shown some positive results in the treatment of axSpA. Apremilast is an oral phosphodiesterase 4 inhibitor that modulates inflammatory

cytokines. It was evaluated in a double-blind, placebo-controlled, phase II study over 12 weeks in 38 patients with symptomatic AS with active disease on MRI. This small pilot study did not meet its primary end point; however Apremilast was associated with improvement in various clinical assessments including BASDAI, BASFI, and BASMI compared to placebo (90). A subsequent phase III multicentre, randomised trial assessing the efficacy and safety of Apremilast in active AS has been completed (NCT01583374). The results of which have not yet been published but preliminary online reports suggest a failure of Apremilast to meet the primary end point (ASAS 20 at week 16) (source: NCT01583374 study results, accessed 1 October 2017).

Tofacitinib is an oral Janus-kinase (JAK) inhibitor, which has proven to be effective in RA(91) and potentially might be also effective in axSpA. A phase II study of Tofacitinib in active AS has shown greater clinical efficacy compared with placebo in ASAS20 and other secondary endpoints in patients with active AS(92). Despite these positive results, the company that owns Tofacitinib has decided to discontinue their programme in axSpA. Another JAK inhibitor, Filgotinib, is currently being investigated for its safety and efficacy in AS (NCT03117270).

Table 3. Novel biologics and Janus-kinase (JAK) inhibitors in clinical trials in axSpA

Drug	Mechanism of action	Study Design	Patients	Trial number
Ustekinumab	monoclonal antibody - blocks IL23 and IL12 by binding to the common p40 subunit	Phase 3 multi-center, DB RCT	axSpA	NCT02437162 NCT02438787 NCT02407223
Ixekizumab	humanized monoclonal antibody against IL 17A	Phase 3 multi-center, DB RCT	axSpA	NCT02696785 NCT02696798 NCT02757352 NCT03129100
Bimekizumab	monoclonal antibody inhibits IL-17A and IL-17F	Phase 2B multi center DB RCT	AS	NCT02963506 NCT03215277
Brodalumab	monoclonal antibody binds to the IL-17 receptor	Phase 3 multi-center, DB RCT	axSpA	NCT02985983
Risankizumab	humanized monoclonal antibody against IL-23A	Phase 2, DB RCT	AS	NCT02047110
BCD085	humanised monoclonal antibody which targets IL-17	International multi-center DB RCT	AS	NCT02763111
Filgotinib	selective JAK1 inhibitor	Phase 2, DB RCT	AS	NCT03117270

DB double-blind, RCT randomised controlled trial, IL interleukin

7. Expert opinion

We have witnessed a great improvement in the treatment of axSpA in the last few years. The future remains exciting for patients with axSpA and for clinicians treating these patients. For the first time in many years a new therapeutic approach has been approved (Secukinumab) and others show promise in axSpA, including small targeted molecules, such as JAK inhibitors. Despite the attention paid to biologic treatments, it is important to emphasise that NSAIDs continue to be the first-line treatment for patients with axSpA and that non-pharmacological treatment modalities are important in the management of these patients (exercise, physical therapy, smoking cessation).

Biosimilars are here to stay and may increase access to effective but expensive biologic therapies, with a desired positive impact on drug expenditures. This is a highly regulated area and current evidence has reduced the initial uncertainty about their use. Switching from bio-originator to biosimilar and extrapolation from one rheumatological indication to other diseases is now widely accepted given the significant amount of evidence that has accumulated about the safety and efficacy of biosimilars. However, switching should be based on a shared decision-making process between patients and rheumatologists, and should take healthcare systems' contextual factor into account. Some concern remains about multiple switching between biosimilars and their bio-originators or other biosimilars. Importantly, harmonised methods are being suggested and established to obtain reliable pharmacovigilance data, including traceability about both biosimilars and bio-originators (93).

Trying to establish which patients benefit the most from each drug is a challenge for the future. There are very few head to head studies comparing the efficacy of biologics in patients with axSpA. Giardina et al investigated Etanercept versus Infliximab in the treatement of AS and found a significantly more rapid clinical improvement in the infliximab treated group (94). However, this is the only head to head study and further studies need to be carried out to test this finding. Selection of biologics may be dependent on patients' preferences/lifestyle and clinical characteristics should be considered, namely the presence of certain extra-articular features. Monoclonal antibodies (Adalimumab, Infliximab and Certolizumab; no data on Golimumab) have been shown to be efficacious in preventing the recurrence of uveitis and in the treatment of inflammatory bowel disease (IBD), whereas Etanercept has shown contradictory results for uveitis, less efficacy in psoriasis and is not efficacious in IBD (95)(96)(97)(98)(73)(99)(100)(101). On the other hand, Etanercept seems to have a lower tuberculosis risk compared to monoclonal antibody TNF-blockers(102). Data suggest that Secukinumab should be avoided in patients with active IBD, as Secukinumab in comparison to placebo was not efficacious in Crohn's disease and resulted in more adverse events (103). It remains to be conclusively shown if any of these drugs will be able to stop or delay radiographic progression.

Highlights Box: Biologics in axial spondyloarthritis

Biologics in axial spondyloarthritis:

1. Significant advances have been made in the treatment of axSpA.
2. Despite the efficacy of biologics, NSAIDs continue to be the first-line treatment for patients with axSpA, and non-pharmacological treatment modalities continue to be important in the management of these patients.
3. For the first time in many years a new therapeutic approach has been approved (targeting IL-17) and others show promise in axSpA.
4. The introduction of biosimilars has greatly reduced the cost associated with biologic treatment.
5. Trying to establish which patients benefit the most from each drug is a challenge for the future.

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