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Effects of biological therapy tapering in the radiographic progression of patients with RA, PsA and axSpA

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Abstract

Introduction: Biological disease-modifying anti-rheumatic drugs (bDMARDs) are one of the greatest means of managing outcomes of patients with severe rheumatological conditions. The concept of drug tapering consists of slowly decreasing the dose of a drug being taken over time to a possible effective minimum while closely watching for a possible increase in disease activity or structural damage progression, aiming for potential gains in safety (reducing drug side effects), costs, and convenience for the patient.

Aim: To determine the rate of radiographic progression in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) patients after 1 to 2 years of progressive biologic tapering according to a standardized protocol.

Methods: A prospective study was carried out to access the radiographic progression in patients with a pre-established diagnosis of RA, PsA (with predominant peripheral (pPsA) or axial (axPsA) involvement), or axSpA undergoing bDMARD therapy tapering. We then determined the mean annual change in structural damage, trying to understand which variables were relevant to the disease's radiographic progression. Our data was registered in and then extracted from the electronic national registry of rheumatic patients (Reuma.pt).

Results: No statistically significant change in structural damage at baseline vs. after 1-2 years of the tapering protocol was observed. It was observed, however, a small trend for radiographic progression in 3 RA patients, 2 pPsA patients, and 5 axSpA/axPsA patients.

Conclusion: After 1-2 years of biologic tapering, small and not statistically significant radiographic progression was found in a minority of RA, PsA, and axSpA patients.

Keywords: bDMARD, tapering, radiographic progression

Resumo

Introdução: Os fármacos biológicos antirreumáticos modificadores da doença (inglês, *bDMARDs*) são um dos melhores meios para gerir doentes com doença reumatológica grave. O conceito de *tapering* consiste na redução lenta da dose de um fármaco até à dose mínima efetiva, monitorizando de perto um possível aumento da atividade da doença ou progressão do dano estrutural, com objetivo de ganhos em segurança (diminuindo efeitos adversos), custos e conveniência para o doente.

Objetivo: Determinar a progressão radiográfica em doentes com artrite reumatoide (inglês, *RA*), artrite psoriática (inglês, *PsA*) e espondilartrite axial (inglês, *axSpA*) após 1 a 2 anos de tapering progressivo de um fármaco biológico seguindo um protocolo standardizado.

Métodos: Realizou-se um estudo prospetivo com objetivo de determinar a progressão radiográfica em doentes com diagnóstico pré-estabelecido de *RA*, *PsA* e *axSpA* (com envolvimento predominantemente periférico (inglês, *pPsA*) ou predominantemente axial (inglês, *axPsA*)) sujeitos a *tapering* de *bDMARD*. Seguidamente determinou-se a variação anual média do dano estrutural, com objetivo de perceber que variáveis seriam relevantes para a progressão radiográfica da doença. Os dados do estudo foram registados e seguidamente extraídos da plataforma eletrónica para registo nacional de doentes reumáticos (Reuma.pt).

Resultados: Não se observou diferença estatisticamente significativa no dano estrutural na *baseline* vs. após 1-2 anos de protocolo de *tapering*. Observou-se, contudo, uma ligeira tendência para progressão radiográfica em 3 doentes com *RA*, 2 com *pPsA* e 5 com *axSpA*/*axPsA*.

Conclusão: Após 1-2 anos de *tapering* de fármaco biológico, observou-se uma ligeiro e não estatisticamente significativa progressão radiográfica numa minoria de doentes com *RA*, *PsA* e *axSpA*.

Palavras-chave: *bDMARD*, *tapering*, progressão radiográfica

Index

Introduction

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) are three distinct immune-mediated rheumatological conditions whose treatment cornerstone remains on modulating the immune pathways involved to achieve remission or low disease activity. This can be obtained either with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) - methotrexate, leflunomide, sulfasalazine, and others – or with targeted therapies such as targeted synthetic DMARDs (tsDMARDs) – apremilast, tofacitinib, and others – and biological DMARDs (bDMARDs) – etanercept, infliximab, and others – designed to interfere with specific mediators of the immune pathways.

Biological drugs are one of the greatest means of managing outcomes of patients with severe rheumatological conditions. Although some of these drugs have already available biosimilars at a lower cost than their originators, their economic burden remains much higher than for most other drugs prescribed in the hospital environment, including csDMARDs.(Bridges et al., 2018) The advent of this type of therapy is not distant in time and as its production requires a considerable amount of technological resources, adding to the relative inconvenience of their parenteral administration and the infectious and immunogenicity risks involved, it is not expectable that they become a first-line DMARD option soon when compared to a csDMARD, still used as a first-line treatment for RA and PsA with polyarthritis.(Gossec et al., 2020; Singh et al., 2015; Smolen, Landewé, et al., 2020)

Similarly, for axial PsA (axPsA) and axSpA, the first option should be a non-steroidal anti-inflammatory drug (NSAID). The criteria for escalating to a biological drug should be, in both cases, the unsuccessful control of disease progression (clinical and/or radiographic) or the inability to maintain remission. In some cases, the use of both csDMARDs and bDMARDs concomitantly might be useful, especially in RA, although further studies are needed to support this regimen in axSpA and PsA.(Gossec et al., 2020; van der Heijde et al., 2017)

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown etiology and is one of the most common inflammatory arthropathies, with an estimated prevalence of 0.7% in Portugal.(Branco et al., 2016) When untreated or resistant to the available therapeutic regimens, it typically leads to deformity and destruction of joints, and consequently to serious disability and incapacity. The diagnosis of RA can be suspected in every adult who presents with a history of chronic symmetric polyarthritis, particularly of the metacarpophalangeal (MCP), metatarsophalangeal (MTP), and/or proximal interphalangeal (PIP) joints. Being a mainly seropositive inflammatory arthritis, high titles (three times normal) of rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (ACPA), the latter being the most specific, are useful to make the diagnosis. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as for other inflammatory conditions, are usually elevated and also support the diagnosis. Radiographic imaging of the affected joints assesses the extent of joint destruction. Bone erosions develop early in the disease course and can already be seen adjacently to the affected joints in approximately 50% of RA patients 12-15 months after the beginning of symptoms.(Machold et al., 2007)

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is an inflammatory, axial and/or peripheral arthritis of unknown etiology usually asymmetric and associated with psoriasis. The diagnosis of PsA can be suspected in every adult who presents with a history of asymmetric oligoarthritis or polyarthritis, often involving the distal interphalangeal (DIP) joints and axial skeleton, in association with psoriasis. Opposite to RA, PsA is usually a seronegative inflammatory arthritis, as only a minority of patients are seropositive for anti-nuclear antibodies (ANAs), RF, and/or ACPA. A common feature in patients with axial PsA is the formation of bony bridges leading to bony fusion (ankylosis), a transformation also seen in ankylosing spondylitis (AS). Enthesitis, tenosynovitis, and dactylitis (sausage digit) are also commonly present in combinations that vary widely from patient to patient.

Extraarticular manifestations such as nail lesions, pitting edema, and uveitis are also common.(Ritchlin et al., 2017)

Axial Spondylarthritis (axSpA)

Axial spondylarthritis (axSpA) is a potentially disabling inflammatory arthritis of the spine and sacroiliac joints usually presenting at younger ages (before the age of 45). Inflammatory back pain, morning stiffness, and progressive loss of spine mobility are the chief clinical manifestations. It is somewhat controversial the distinction between non-radiographic axSpA (nr-axSpA) and AS within the axSpA spectrum, as many of the patients with nr-axSpA later progress to radiographic sacroiliitis, meeting the New York criteria for AS (prior to radiographic changes, inflammation of the sacroiliac joints is only detectable by magnetic resonance imaging).(Linden et al., 1984) It is believed that these two entities are two distinct stages of the same disease. However, most nr-axSpA patients do not progress to a radiographic phase over 10 years (or do so but at an exceptionally slow rate).(Protopopov & Poddubnyy, 2018) Similar to PsA, which is also part of the spondyloarthritides family, a variety of extra-articular manifestations can be present such as enthesitis, tenosynovitis, dactylitis, uveitis, psoriasis, and inflammatory bowel disease. A useful diagnostic feature is the presence of human leukocyte antigen B27 (HLA-B27), found in more than 90% of the patients with SpA but also found in approximately 8% of healthy individuals.(Sieper & Poddubnyy, 2017)

Biological Therapy Tapering

Similar to prescribing other types of medicines, a biological therapy regimen should obey the same pharmacological and ethical principles respecting terms for the least dosage and for the lesser time possible, sufficient to ensure disease remission or control. As such, the concept of drug tapering comes in order. Tapering consists of slowly decreasing the dose of the drug being taken over time to a possible effective minimum while closely watching for a possible increase in disease activity or structural damage progression. The aim is to achieve potential gains in safety (reducing drug side effects), costs, and convenience for the patient.

Disease activity changes over time and effective treat-to-target management of RA often achieves a long-standing disease remission state, after early aggressive treatment of active disease, that no longer requires such intensive treatment to be maintained.(Fautrel & den Broeder, 2015) It has long been common practice to taper csDMARDs to the lowest effective dose. In contrast, bDMARDs are often used in more aggressive disease and were approved for use with a single, universal dosage (except for infliximab, which is adjusted to the patient's weight but not to disease severity). Consistently, tapering bDMARDs has been regarded with greater caution but evidence has accumulated that it can also be performed safely in a large proportion of RA, PsA, and axSpA patients. Although an increase in flare rate is often observed while tapering bDMARDs, these flares may not impact long-term disability and radiographic progression as long as they are short-lived and remission is regained with reinstitution of the previous effective dose.(Kuijper et al., 2015; Stamp et al., 2019; Tanaka & Hirata, 2013)

Tapering bDMARDs in RA, PsA, and axSpA should only be performed in patients in long-standing remission to minimize the risk of flare.(Smolen, Pedersen, et al., 2020) In this setting, the decrease can exceed 50% of the approved dose, although complete withdrawal of bDMARD is rarely possible.(Schett et al., 2016) Randomized controlled trials of bDMARD tapering strategies have only been performed in RA, and more data is still needed to support bDMARD tapering in PsA and axSpA.

One important concern is the possibility of subclinical structural damage taking place more often in patients who tapered bDMARDs, even if clinical remission is maintained, which may cause further disability in the long run.(Schett et al., 2016) Using radiographic progression as a reliable tool for the evaluation of overall disease progression, and taking into account the economic burden and patient convenience underlying the usage of biological drugs, the hypothesis of this clinical investigation rises – is there any or substantial radiographic progression, in clinically stable patients, when undergoing tapering of biological drugs? A complete discussion of our findings follows.

Methods

We carried out a prospective study to access the radiographic progression in patients with a pre-established diagnosis of RA, PsA, or axSpA undergoing bDMARD therapy tapering. We then determined the mean annual change in structural damage and probability of radiographic disease progression, trying to understand which variables were relevant for the disease radiographic progression.

Patients were enrolled in an open cohort; patient recruitment started in January 2019 and data extraction for analysis happened in July 2021. All of the used data was registered in and then extracted from the electronic national registry of rheumatic patients (Reuma.pt).

The present study had the approval of the CAML (*Centro Académico de Medicina de Lisboa*) Ethics Commission.

Disease Activity

To assess disease activity two different scores were used: DAS28-4V-ESR for RA and predominantly peripheral PsA patients, and ASDAS-CRP for axSpA and predominantly axial PsA patients. For PsA, disease activity was measured according to their main clinical involvement being axial or peripheral (as reported by the attending rheumatologist). DAS28-4V-ESR, (28-joint Disease Activity Score) accounts for 4 variables: 28 tender (TJC28) and swollen (SJC28) joint counts, patient global assessment of disease activity (using a numerical rating scale (NRS) of 0 to 10, asked orally) and erythrocyte sedimentation rate (ESR). Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) is computed from the patient's global assessment of disease activity (on a 0-10 NRS), the responses to questions 2, 3, and 6 from the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on the severity of back pain, peripheral pain/swelling and duration of morning stiffness (on a 0-10 NRS), and the CRP value (in mg/L).(van der Heijde et al., 2009; van Riel & Renskers, 2016)

Inclusion Criteria

Patients eligible for this study had to be in persistent remission while on a biological therapy regimen (concomitant csDMARD therapy was admitted). This was evaluated with DAS28-4V-ESR and ASDAS scores. The persistent remission threshold was, for RA and predominantly peripheral PsA patients, a DAS28-4V-ESR less than 2.6 in the last 12 months (DAS28 remission), and for axSpA and predominantly axial PsA patients, an ASDAS less than 2.1 in the last 12 months (ASDAS low disease activity).

The bDMARDs subjected to tapering in this study were infliximab (IFX), golimumab (GOL), certolizumab pegol (CTZ), and adalimumab (ADA) – all monoclonal antibodies to tumor necrosis factor (TNF), etanercept (ETN) – a recombinant protein of the soluble TNF receptor and human immunoglobulin Fc fragment, and tocilizumab (TCZ) – a monoclonal antibody to the interleukin 6 receptor (IL-6R).

Tapering Protocol

The tapering protocol in this study followed the increasing the interval between doses principle.(González-Álvaro et al., 2015) Patients who met the inclusion criteria and consented to participate were asked to increase the regular interval (RI) between biologic administration by 50% (1.5xRI). If remission was maintained after 6 months, the dosing interval was increased again to twice the regular interval (2xRI). In the case of disease flare (defined as DAS28>2.6, ASDAS>2.1, or any increase in disease activity justifying a change of treatment by the attending physician), the previous treatment frequency was reintroduced by protocol.

Disease activity and patient-reported outcomes were assessed every 3 months; function, health-related quality of life, peripheral joint ultrasound, radiographs, serum drug levels, and anti-drug antibodies were assessed at baseline and 1 year.

Radiographic Analysis

AxSpA and predominantly axial PsA patients performed a set of lateral radiographs of the cervical and lumbar spine and anteroposterior radiographs of the pelvis. RA and predominantly peripheral PsA patients performed posteroanterior radiographs of the

hands and feet. Radiographs were taken at the beginning of the study (baseline) and after 12-24 months of bDMARD tapering.

All the available radiographs were then scored by two distinct evaluators using 3 validated scores (attachments A, B, and C): the Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), the Sharp/van der Heijde Score for Rheumatoid Arthritis (SvdH), and the Sharp/van der Heijde Modified Scoring Method for Psoriatic Arthritis (SvdH PsA). The evaluators were blind for the patient identification and rated the exams according to their chronological order.

Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

This scoring method (attachment A) is a modification of the score originally described by Taylor et al., which recommends scoring each upper and lower anterior vertebral edge from the lower border of the 2nd cervical vertebra to the upper border of the 1st thoracic vertebra and from the lower border of the 12th thoracic vertebra to the upper border of the sacrum as follows: 0 = no abnormality; 1 = erosion and/or sclerosis and/or squaring; 2 = syndesmophyte (non-bridging); 3 = total bony bridging between upper and lower vertebral edges (ankylosis). The total mSASSS (range: 0-72) is the sum of scores calculated for the 24 anterior vertebral edges included in the lumbar and cervical scoring system, based on lateral radiographic views of the spine. As an exception, the 3rd cervical vertebra is not scored for squaring.(Creemers et al., 2005) In the event that a given vertebral edge could not be clearly seen, it was classified as a missing observation and the total score (range 0–36) was calculated as 12 times the mean score of all scoring sites for the respective cervical/spinal segment.(van der Heijde et al., 2019) Although this scoring method was developed for the assessment of patients with ankylosing spondylitis (AS), its reliability as a method for scoring axial psoriatic arthritis (axPsA) has been demonstrated.(Ibrahim et al., 2017)

Sharp/van der Heijde Score for Rheumatoid Arthritis (SvdH)

In this scoring method (attachment B), both erosions and joint-space narrowing (JSN) are scored separately: erosions are counted in the 10 metacarpophalangeal (MCP)

joints, the eight proximal interphalangeal (PIP) joints, the two interphalangeal joints of the thumbs, the right and left first metacarpal bone, the right and left radius and ulnar bones, the right and left trapezium and trapezoid (as one unit; multangular), right and left navicular bones, right and left lunate bones, the 10 metatarsophalangeal (MTP) joints, and the two interphalangeal joints of the big toes. JSN is assessed in the 10 MCP joints, the eight PIP joints, right and left third, fourth and fifth carpometacarpal joints, right and left multangular-navicular joints, right and left capitate-navicular-lunate joints, right and left radiocarpal joints, the 10 MTP joints, and the two interphalangeal joints of the big toes. Erosions are scored as follows: 1 = discrete interruption of the cortical surface; 2 = larger lesions but not ranging across the bone midline; 3 = larger lesions ranging across the bone midline; 5 = complete bone collapse or sum of individual lesions equal to/greater than 5. Consequently, for confluent erosions, the score cannot decrease. In the hands, the maximum erosion score in a joint is 5; in the feet, it is 10. For JSN, five grades are recognized: 0 = normal, 1 = focal or doubtful; 2 = general, <50% of the original joint space; 3 = general, >50% of the original joint space or subluxation; 4 = ankylosis. The maximum score of erosions is 160 in the hands and 120 in the feet; and the maximum scores for JSN are 120 and 48, respectively. The total score is the sum of scores for erosions and JSN. The maximum total score is 448.(van der Heijde et al., 1999)

Sharp/van der Heijde Modified Scoring Method for Psoriatic Arthritis (SvdH PsA)

The modification (attachment C) based on the Sharp/van der Heijde method scores the same joints and definitions as seen in RA, with the addition of the distal interphalangeal (DIP) joints of fingers 2 to 5 of both hands. The erosions are scored as follows: 0 = absent; 1 = discrete erosions; 2 = large erosion not ranging across the bone midline; 3 = large erosion ranging across the bone midline; 4/5 = sum of individual lesions adding to 4/5. In the feet, 0–5 scores are calculated for each side (proximal and distal) of the joint therefore the maximum score can reach 10. For JSN, five grades are recognized: 0 = normal; 1 = focal or general narrowing up to a maximum of 25% of the original joint space; 2 = definite narrowing loss of less than 50% of the original joint space; 3 = definite narrowing of more than 50% of the original joint space or subluxation; 4 = no detectable joint space/ankylosis or complete luxation. Gross osteolysis and/or pencil-in-cup

phenomenon are scored separately in the same joints. If present, these characteristics warrant the joint maximum score for both erosions and JSN. The maximum score of erosions is 200 in the hands and 120 in the feet; and the maximum scores for JSN are 160 and 48, respectively. The total score is the sum of scores for erosions and JSN. The maximum total score is 528.(van der Heijde et al., 2005)

Statistical Analysis

For the statistical analysis, we used IBM SPSS Statistics software version 28.0 for macOS. Firstly, we calculated the proportion of patients with score progression, by disease. Secondly, we calculated the mean score progression and then performed paired samples t-tests with scores at baseline and 1-year follow-up and univariate logistic regressions relating the score progression with flare occurrence and maintained tapered dose at 1-year follow-up, for each group of patients (RA, PsA and axSpA). Additionally, we calculated the inter-rater reliability using the intraclass correlation coefficient (ICC) with a two-way mixed-effects model for absolute agreement definition and the smallest detectable change (SDC) using the Bland & Altman method ($SDC=(\pm 1.96 \times SD_{(Baseline\ Score-1Y\ Score)})\div(\sqrt{2}\times\sqrt{k})$, for 95% levels of agreement, k=number of readers, in our study k=2). Radiographic progression was considered to exist when the score change was greater than the calculated SDC.(Koo & Li, 2016; Navarro-Compán et al., 2014) In the case of progression, the score change was compared to the minimal clinically important difference (MCID) as previously defined for the SvdH score (MCID not determined for the mSASSS).(Bruynesteyn et al., 2002)

Results

Patient Characteristics

Of 54 patients with RA, PsA, and axSpA in sustained remission on bDMARDs, who were screened as candidates for tapering, 49 patients (16 RA, 15 PsA, and 18 axSpA) met the inclusion criteria and completed baseline assessment. 11 patients were excluded before they started tapering (9 had clinical flares – 7 of whom were RA patients, 1 had subclinical Doppler+ synovitis on ultrasound, 1 was pregnant). The remaining 38 patients initiated tapering and had a mean follow-up (±SD) of 21.1(±7.6) months. 30 patients had

new radiographs performed at 12-24 months of follow-up. The reasons for not having follow-up radiographs were lack of compliance (n=4, mainly due to fear of hospital-related SARS-CoV-2 infection), prescription error (n=2), and data export prior to the programmed radiograph (n=2). The studied population of 30 individuals, 9 female (30%) and 21 male (70%), 7 had the diagnosis of RA (23,3%), 9 of PsA (30%), and 14 of axSpA (46,7%). The mean age at baseline was 54 years (32 to 78 years). One PsA patient had both significant peripheral and axial involvement. He was assessed for radiographic progression in both domains; axial disease scores were analyzed together with axSpA patients.

Accounting for bDMARD therapy regimens, infliximab was received by 2 patients (6,7%), golimumab by 8 (26,7%), adalimumab by 8 (26,7%), etanercept by 6 (20%), tocilizumab by 5 (16,7%), and certolizumab pegol by 1 (3,3%). At baseline, all patients were receiving bDMARD at the standard dose and 16 (53,3%) were under bDMARD monotherapy. Concomitant csDMARD therapy was received by 14 patients (46,7%): 11 methotrexate (36,7%) and 3 sulfasalazine (10%), at variable doses.

Table 1 Baseline demographic and disease characteristics of the study population

	RA (n=7)	PsA (n=9)	axSpA (n=14)
Age, years, mean (SD)	59,1 (6,2)	56,4 (9,9)	49,5 (12,6)
Male gender, n (%)	1 (14,3)	9 (100)	11 (78,6)
Predominant axial involvement, n (%)	-	1 (11,1)	14 (100)
Enthesitis, n (%)	-	6 (66,7)	8 (57,1)
Disease activity, mean (SD)			
Axial (ASDAS)	-	1,50 (-)	1,26 (0,53)
Peripheral (DAS28)	1,93 (0,35)	1,09 (0,68)	-
Physical function, median (IQR)			
BASFI	-	0,35 (-)	0,76 (3,18)
HAQ	0,00 (0,13)	0,00 (0,00)	-
Biological DMARD			
Infliximab, n (%)	-	-	2 (14,3)
Golimumab, n (%)	1 (14,3)	5 (55,6)	2 (14,3)
Adalimumab, n (%)	-	3 (33,3)	5 (35,7)
Etanercept, n (%)	1 (14,3)	1 (11,1)	4 (28,6)
Tocilizumab, n (%)	5 (71,4)	-	-
Certolizumab, n (%)	-	-	1 (7,1)
Conventional Synthetic DMARD			
Methotrexate, n (%)	5 (71,4)	5 (55,6)	1 (7,1)
Sulfasalazine, n (%)	1 (14,3)	-	2 (14,3)

SD, Standard Deviation; RA, Rheumatoid Arthritis; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASFI, Bath Ankylosing Spondylitis Functional Index; DAS28, 28-joint Disease Activity Score; HAQ, Health Assessment Questionnaire; IQR, interquartile range; PsA, psoriatic arthritis

Rheumatoid Arthritis Patients' Outcomes

The inter-rater reliability test for SvdH score revealed an ICC for average measures of 0,998 [95% CI (0,995-0,999); p = <0,001], indicating excellent inter-rater reliability. For this scoring method, the SDC was 1,7 units. The Bland-Altman plot showed the mean bias ±SD between observers 2 and 1 as -0,14 ±1,61 units, and the limits of agreement were −3,30 and 3,01.(figure 2, attachment D).

At 1 year follow-up, bDMARD dose had been successfully tapered in 5 (71,4%) RA patients, with 2 (28,6%) receiving bDMARD at the regular interval (RI) plus 50% (1.5xRI) and 3 (42,9%) at twice the regular interval (2xRI), while 2 (28,6%) were receiving the standard dose.

Flare was eventually observed in all 7 RA patients (100%), after 10,9 ±6,8 months: 4 (57,1%) flared at 1.5xRI and 3 (42,9%) at 2xRI. Flare recovery occurred with no change in bDMARD dosage in 2 patients (28,6%) (flare deemed unrelated to disease activity by the attending physician) but required reinstitution of the standard dose in 5 patients (71,4%).

All 7 patients (100%) were in remission at 1 year follow-up (DAS28-4V < 2.6). Using the Sharp van der Heijde Score and calculated SDC we observed radiographic progression (RP) in 3 (42,9%) patients. Overall mean RP was 1,43 ±2,17, from 10,64 ±16,79 at baseline to 12,07 ±17,60 at 1 year follow-up (difference not statistically significant, p = 0.13). RP occurred in 2/5 (40%) of patients keeping a tapered dose at 1 year, and in 1/2 (50%) patients among those who returned to the approved dose. Additionally, both hands and feet scores were analyzed separately, with a hands' mean RP of 0,14 ±0,63 (p = 0,57) and feet's mean RP of 1,29 ±1,98 (p = 0,14). Patients whose change was larger than the SDC had more damage at baseline, although the difference was not statistically significant (SvdH=19.5 vs. 4.0, p=0.26).

Table 2 Results of paired samples t-test for RA patients

	Mean change	SD	SEM	p-Value
Hands' Score at 1 Year - Hands' Score at BS	0,143	0,626	0,237	0,569
Feet's Score at 1 Year - Feet's Score at BS	1,286	1,976	0,747	0,136

Total Score at 1 Year - Total Score at BS	1,429	2,169	0,820	0,132

Significant values are shown in bold typeface. BS, Baseline; SD, Standard Deviation; SEM, Standard Error Mean

Since all RA patients flared during the study, flaring was not a considerable variable to relate to RP. The relation between RP and tapered dose at 1 year was also analyzed using a univariate logistic regression. Tapered dose at 1-year follow-up was not significantly associated with the likelihood of RP (p = 0,81).

Table 3 Results of univariate logistic regressions for prediction of radiographic progression in RA patients

	OR	OR (95% CI)	p-Value
Tapered dose at 1Y	0,667	0,025 – 18,059	0,810

Significant values are shown in bold typeface. OR, odds ratio; CI, confidence interval

Peripheral Psoriatic Arthritis Patients' Outcomes

The inter-rater reliability test for SvdH PsA score revealed an ICC for average measures of 0,998 [95% CI (0,997-0,999); p = <0,001], indicating excellent inter-rater reliability. For this scoring method, the SDC was 1,0 units. The Bland-Altman plot showed the mean bias ±SD between observers 2 and 1 as -0,22 ±0,65 units, and the limits of agreement were −1,49 and 1,05.(figure 4, attachment D).

At 1 year follow-up, bDMARD dose had been successfully tapered in 6 (66,7%) PsA patients, with 3 (33,3%) receiving bDMARD at the regular interval (RI) plus 50% (1.5xRI) and 3 (33,3%) at twice the regular interval (2xRI), while 3 (33,3%) were receiving the standard dose.

Flare was eventually observed in 5 PsA patients (55,6%), after 5,6 ±5,5 months: 4 (44,4%) flared at 1.5xRI and 1 (11,1%) at 2xRI. Flare recovery occurred with no change in bDMARD dosage in 1 patient (11,1%) but required reinstitution of the standard dose in 4 patients (44,4%).

All 9 patients (100%) were in remission at 1-year follow-up (DAS28-4V < 2.6, or ASDAS < 1.3 for the one patient scored for both peripheral and axial disease).

Using the Sharp van der Heijde Score and calculated SDC we observed radiographic progression (RP) in 2 (22,2%) patients. Overall mean RP was 0,33 ±1,12 from 7,78 ±8,70 at baseline to 8,11 ±9,61 at 1 year follow-up (difference not statistically significant, p =

0.40). RP occurred in 1/6 (16,7%) patients keeping a tapered dose at 1 year, and in 1/3 (33,3%) patients among those who returned to the approved dose. Additionally, both hands and feet scores were analyzed separately, with a hands' mean RP of 0,00 ±0,50 (p = 0,9(9)) and feet's mean RP of 0,33 ±1,00 (p = 0,35). Patients whose change was larger than the SDC had significantly more damage at baseline (SvdH=20.5 vs. 4.1, p<0,01).

Table 4 Results of paired samples t-test for PsA patients

	Mean change	SD	SEM	p-Value
Hands' Score at 1 Year - Hands' Score at BS	0,000	0,500	0,167	0,99(9)
Feet's Score at 1 Year - Feet's Score at BS	0,333	1,000	0,333	0,347
Total Score at 1 Year - Total Score at BS	0,333	1,118	0,373	0,397

Significant values are shown in bold typeface. BS, Baseline; SD, Standard Deviation; SEM, Standard Error Mean

The relation between RP and flare occurrence and tapered dose at 1 year was also analyzed using univariate logistic regressions. Flare occurrence was not significantly associated with the likelihood of RP (p = 0,86). Tapered dose at 1-year follow-up was not significantly associated with the likelihood of RP (p = 0,58).

Table 5 Results of univariate logistic regressions for prediction of radiographic progression in pPsA patients

	OR	OR (95% CI)	p-Value
Flare occurrence	0,750	0,032 – 17,506	0,858
Tapered dose at 1Y	0,400	0,016 – 10,017	0,577

Significant values are shown in bold typeface. OR, odds ratio; CI, confidence interval

Axial Spondyloarthritis and Axial Psoriatic Arthritis Patients' Outcomes

The inter-rater reliability test for mSASSS revealed an ICC for average measures of 0,998 [95% CI (0,999-1,000); p = <0,001], indicating excellent inter-rater reliability. For this scoring method, the SDC was 0,9 units. The Bland-Altman plot showed the mean bias ±SD between observers 2 and 1 as -0,10 ±1,10 units, and the limits of agreement were −2,26 and 2,07.(figure 6, attachment D).

At 1 year follow-up, bDMARD dose had been successfully tapered in 11 (73,3%) axSpA/axPsA patients, with 3 (20,0%) receiving bDMARD at the regular interval (RI) plus

50% (1.5xRI) and 8 (53,3%) at twice the regular interval (2xRI), while 4 (26,7%) were receiving the standard dose.

Flare was eventually observed in 8 axSpA/axPsA patients (53,3%), after 8,8 ±4,8 months: 4 (26,7%) flared at 1.5xRI, and 4 (26,7%) at 2xRI. Flare recovery required reinstitution of the bDMARD 1.5xRI in 2 patients (13,3%), standard dose in 5 patients (33,3%), and in 1 patient (6,7%) recovery was not achievable with standard dose and bDMARD switch was needed.

Inactive disease at 1 year follow-up (ASDAS < 1.3) was observed in 9 patients (60,0%), 4 (26,7%) had low disease activity (ASDAS < 2.1), 1 (6,7%) high disease activity (2.1 < ASDAS < 3.5), and 1 (6,7%) very high disease activity (ASDAS > 3.5).

Using the Modified Stoke Ankylosing Spondylitis Spinal Score and calculated SDC we observed radiographic progression (RP) in 5 (33,3%) patients. Overall mean RP was 0,55 ±1,09 from 17,46 ±22,35 at baseline to 18,01 ±22,50 at 1 year follow-up (difference not statistically significant, p = 0.07). RP occurred in 4/7 (57,1%) patients keeping a tapered dose at 1 year, and in 1/4 (25,0%) patients among those who returned to the approved dose. RP occurred in 3/8 (37,5%) patients who had a disease flare, and in 2/7 (28,6%) patients who had no flare. Patients whose change was larger than the SDC had more damage at baseline (mSASSS=20.4 vs. 16.0, p=0.73), although the difference was not statistically significant.

Table 6 Results of paired samples t-test for axSpA/axPsA patients

	Mean change	SD	SEM	p-Value
mSASSS at 1 Year - mSASSS at BS	0,550	1,086	0,281	0,070

Significant values are shown in bold typeface. BS, Baseline; SD, Standard Deviation; SEM, Standard Error Mean

The relation between RP and flare occurrence and tapered dose at 1 year was also analyzed using univariate logistic regressions. Flare occurrence was not significantly associated with the likelihood of RP (p = 0,72). Tapered dose at 1-year follow-up was not significantly associated with the likelihood of RP (p = 0,68).

Table 7 Results of logistic regressions for prediction of radiographic progression in axSpA/axPsA patients

	OR	OR (95% CI)	p-Value
Tapered dose at 1Y	1,714	0,131 – 22,513	0,682
Flare occurrence	1,500	0,170 – 13,225	0,715

Significant values are shown in bold typeface. OR, odds ratio; CI, confidence interval

Discussion

In this study, our primary outcome was radiographic progression in RA, PsA, and axSpA patients in remission under a bDMARD therapy tapering protocol over a follow-up period of 1 year. When possible, radiographs were taken at the moment of a medical appointment and there were significant delays due to the COVID-19 pandemic, which resulted in the follow-up radiographs being performed 12-24 months after the start of bDMARD tapering.

Clinicians are facing an increasing number of patients achieving sustained remission with the use of bDMARDs, dose tapering (or even discontinuation, not approached in this study) is therefore increasingly being considered and recommended by 2019 EULAR recommendations for the management of RA and PsA, and 2016 for axSpA.(Brahe et al., 2019; Gossec et al., 2020; Smolen, Landewé, et al., 2020; van der Heijde et al., 2017) When facing axSpA alone, however, 2019 updated recommendations from the American College of Rheumatology (ACR) are against tapering the bDMARD in stable axSpA patients.(Ward et al., 2019) The level of evidence for such recommendations is low to very low, and the economic burden, infectious risk, and patient inconvenience associated with supra-therapeutic bDMARD dosage, as mentioned earlier, stress the need for further research about the clinical and radiographical impact of tapering biological drugs.

When reviewing literature for biological therapy tapering studies, publications involving RA patients stand out, by far. In a 2016 review in the Annals of Rheumatic Diseases (ARD), 11 tapering studies were presented as having a percentage of successful bDMARD tapering up to 79% in a 0,5 to 1,5-year follow-up, in RA patients.(Schett et al., 2016) They concluded that the available evidence suggested that tapering bDMARD/tsDMARD was a feasible strategy in a subset of patients with RA who had

entered clinical remission. The same conclusion (for tumor necrosis factor inhibitors, TNFi, only) was published in a Cochrane Review in 2019 adding that a tapering strategy is comparable to the continuation of the standard dose regarding disease activity, but possibly not in function and radiographic progression, although the latter is supported by not statistically significant results.(Verhoef et al., 2019) The same robust conclusions are not yet available for PsA and axSpA, however. A 2018 review article addressed the outcomes of 6 bDMARD tapering studies in PsA patients and concluded that tapering might be feasible and safe in patients with PsA who are in remission or with low disease activity.(Ye et al., 2018) Very limited literature addressed bDMARD tapering protocols in axSpA patients. The first study to be published in 2019 and concerning axSpA patients only, despite all its limitations, supported the non-inferiority of reduced TNFi doses compared with full doses in axSpA patients.(Gratacós et al., 2019)

Adding to the fact that few studies address the efficacy of bDMARD tapering strategies, even less study disease RP as an outcome. Of two robust meta-analyses comparing a total of 11 studies discussing bDMARD tapering after achieving LDA or remission in RA, only 5 reported RP outcomes, agreeing that differences in RP values are minimal and have questionable value in terms of the clinical relevance. In addition, the pooled RP calculated in both meta-analyses was not statistically significant.(Henaux et al., 2018; Verhoef et al., 2019) As expected, our results did not demonstrate a substantial radiographic progression (RP) in any of the subgroups (RA, PsA, and axSpA) of patients. It is important to stand out that the SDCs calculated in our study are lower than the SDCs already published with the respective scoring method, and that is due, presumably, to our very high ICC for every scoring method, justified by the considerable amount of patients scored with 0 (or close to) since most of our population had little radiographic damage at baseline.(Navarro-Compán et al., 2014; Ramiro et al., 2013) This relation suggests that the rate of RP observed in our study, in terms of the proportion of RP larger than the SDC, might be attributed to the scoring process itself.

When comparing the smallest detectable difference (SDD) for SvdH scores and mSASSS proposed by other studies (not related to bDMARD tapering protocols) with larger populations, we observed no RP greater than 5, 11, and 2 score units for RA, PsA, and axSpA respectively.(Baraliakos et al., 2009; Bruynesteyn et al., 2002; Tillett et al., 2014).

As for the minimal clinically important difference (MCID), it was only established for the SvdH score in RA.(Bruynesteyn et al., 2002) An RP of 5 units (same as SDD) was proposed as the threshold of RP which would require medical intervention. In our study, there were no RA or PsA patients showing an SvdH score progression larger than the MCID, further supporting that the observed progression is small and has questionable clinical significance.

We also tried to assess the relation of RP to flare occurrence and duration of drug tapering (maintenance of a tapered dose at 1 year) but neither of these variables seemed to affect positively nor negatively RP during our timeline. These conclusions, although conditioned by the study limitations, seem to suggest that RP might be related to other intrinsic factors of the individual and/or disease, such as previous radiographic damage, as we observed that a greater RP occurred in patients (all subgroups) with a higher score (and therefore higher radiographic damage) at baseline.

Future clinical studies are ongoing to provide evidence of the effectiveness and safety of bDMARDs tapering strategies, especially in patients with PsA and axSpA, as well as to provide predictors for the eventual loss of remission.

Limitations

The main limitation of this study is the sample size, which limits the external validity of our findings and the ability to study predictors of RP in multifactorial regression models. Other limitations are the unavailability of post-tapering radiographs for additional 8 patients who completed the baseline assessment and 1 year of follow-up but could not be included in this analysis, and the relatively short follow-up period. Disease progression is slow (mean SvdH score change of 0.75 at 18 months, in RA) and significant changes may require long follow-up to be detected.(van Herwaarden et al., 2015) In addition, the flare rate was relatively constant over time and 6/20 (30,0%) flares occurred more than 1 year after the start of bDMARD tapering, indicating that possible structural progression might be occurring due to treatment failure later than the radiographic timepoint analyzed here.(Ávila Ribeiro et al., 2021) Further radiographic assessment of this cohort is needed to ascertain late disease progression.

Conclusion

Overall, our study revealed that small and not statistically significant radiographic progression occurred in a minority of RA, PsA, and axSpA patients undergoing a biological therapy tapering protocol, despite the occurrence of frequent disease flares, irrespective of the tolerance of tapered bDMARD dose over 1 year.

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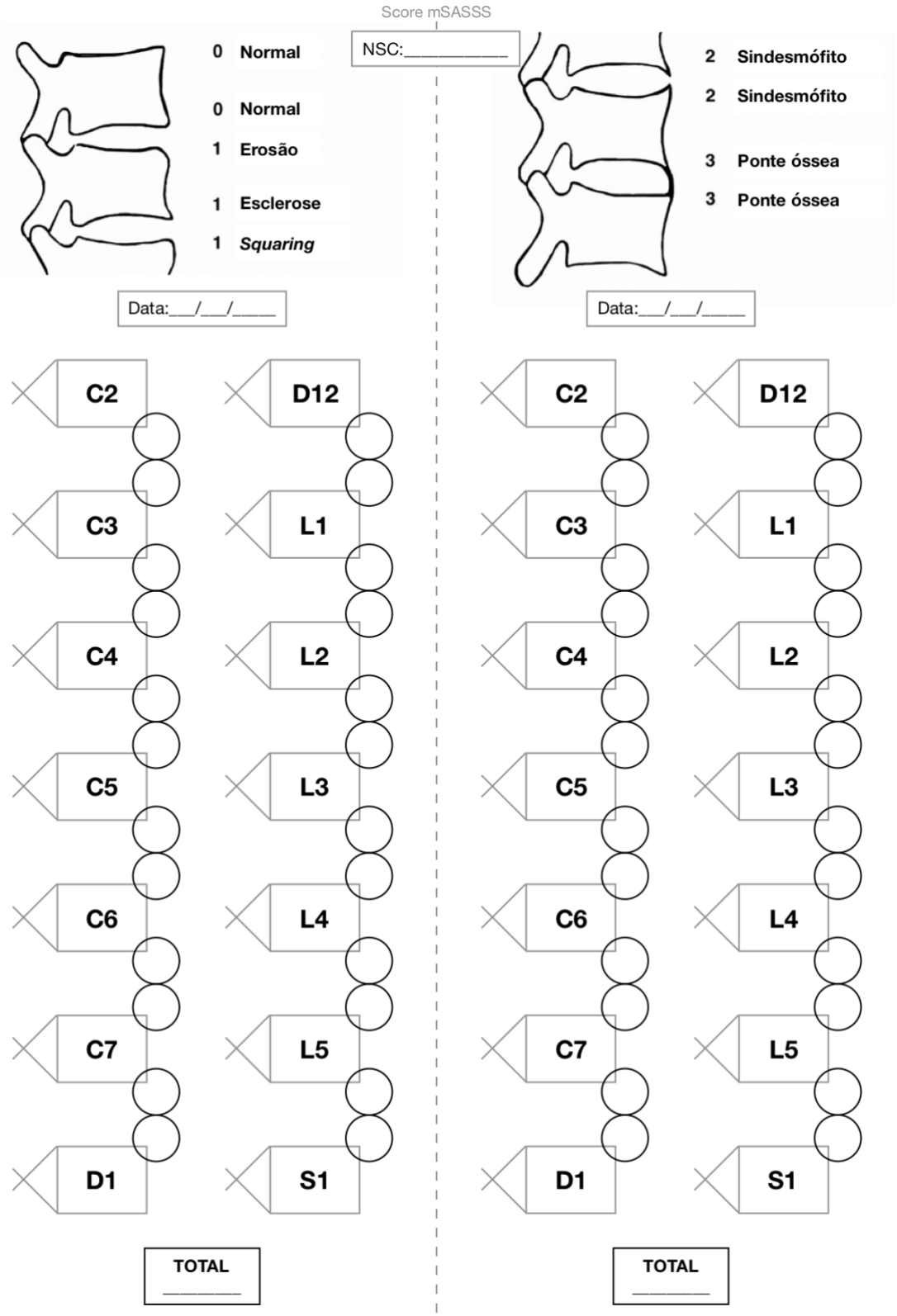
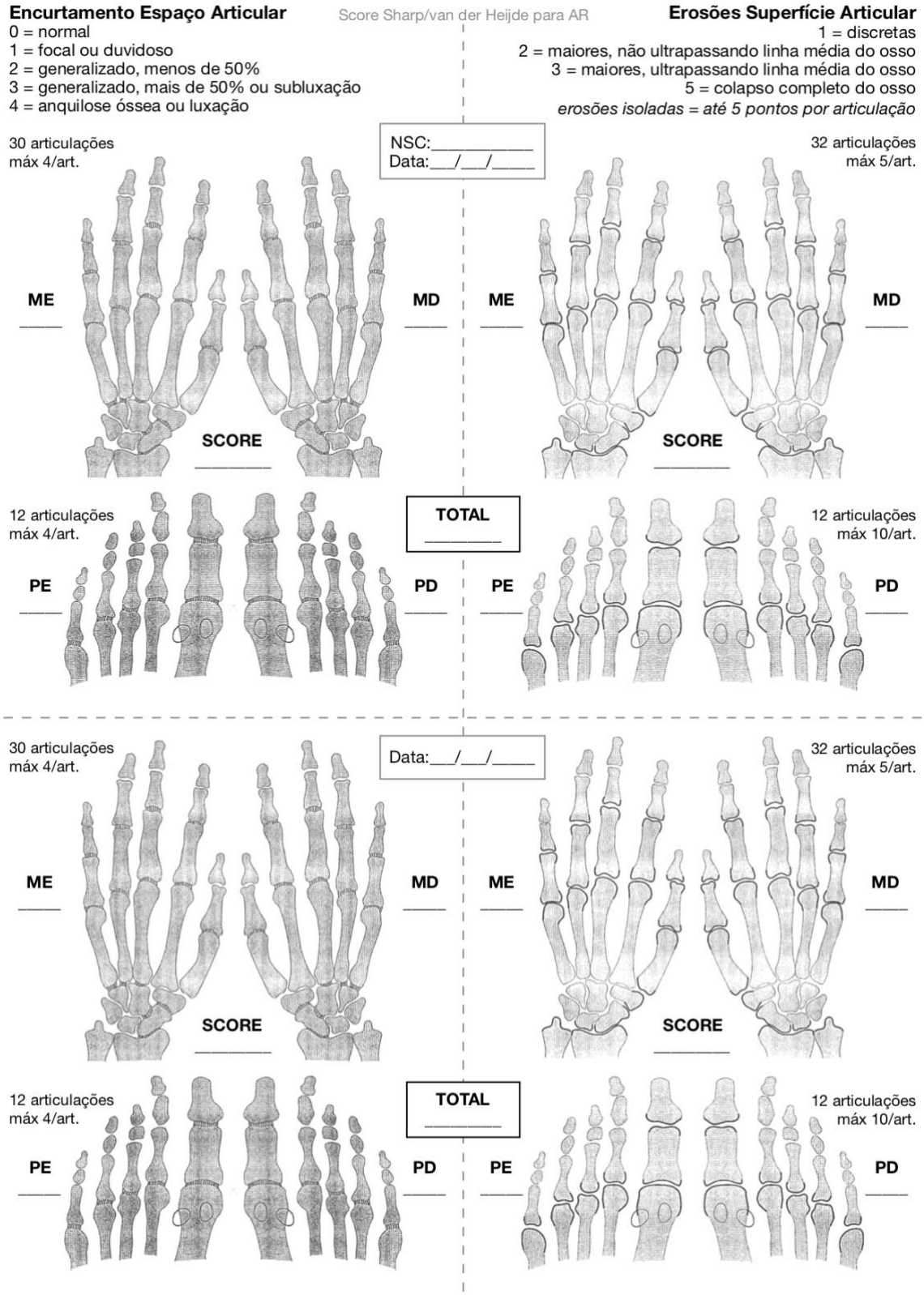
Attachments

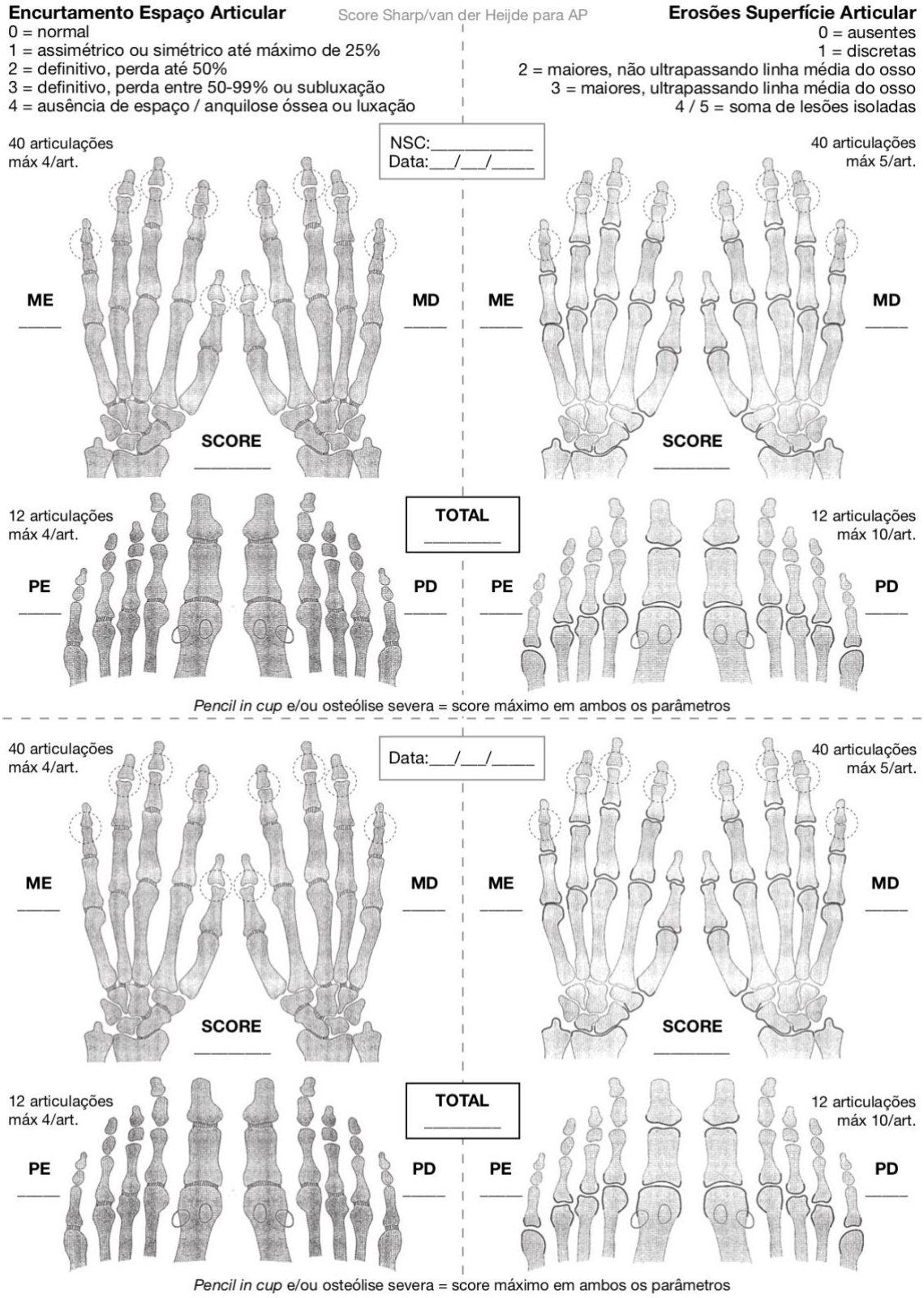
Attachment A



Attachment B



Attachment C



Attachment D

Figure 1 Scatter-plot of observers 1 and 2 total SvdH score at baseline and at 1 year follow-up (RA)

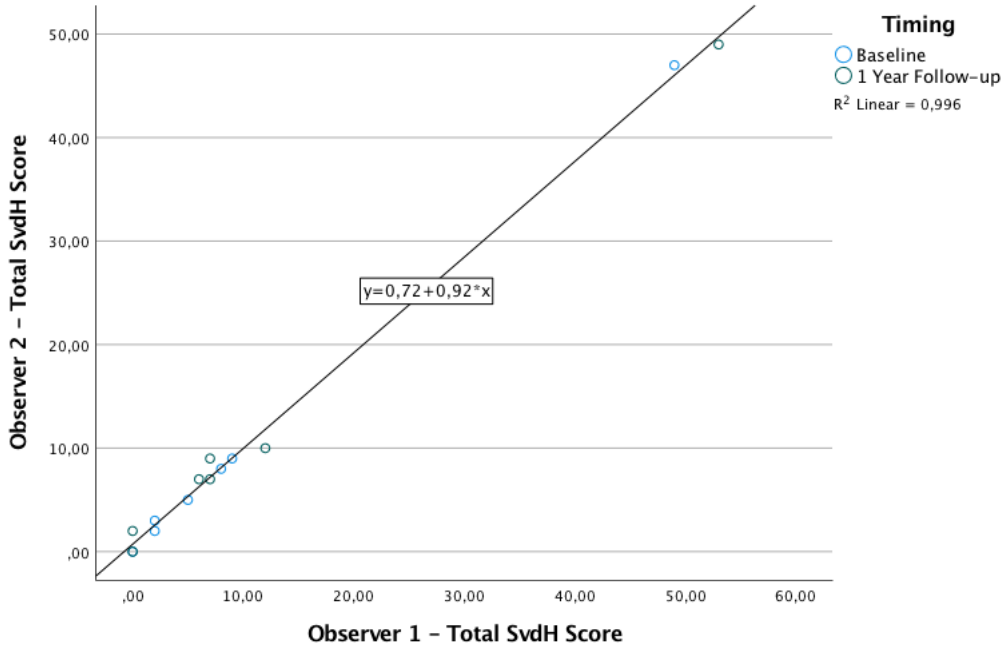


Figure 2 Bland-Altman plot of observers 1 and 2 rating difference t-test (RA)

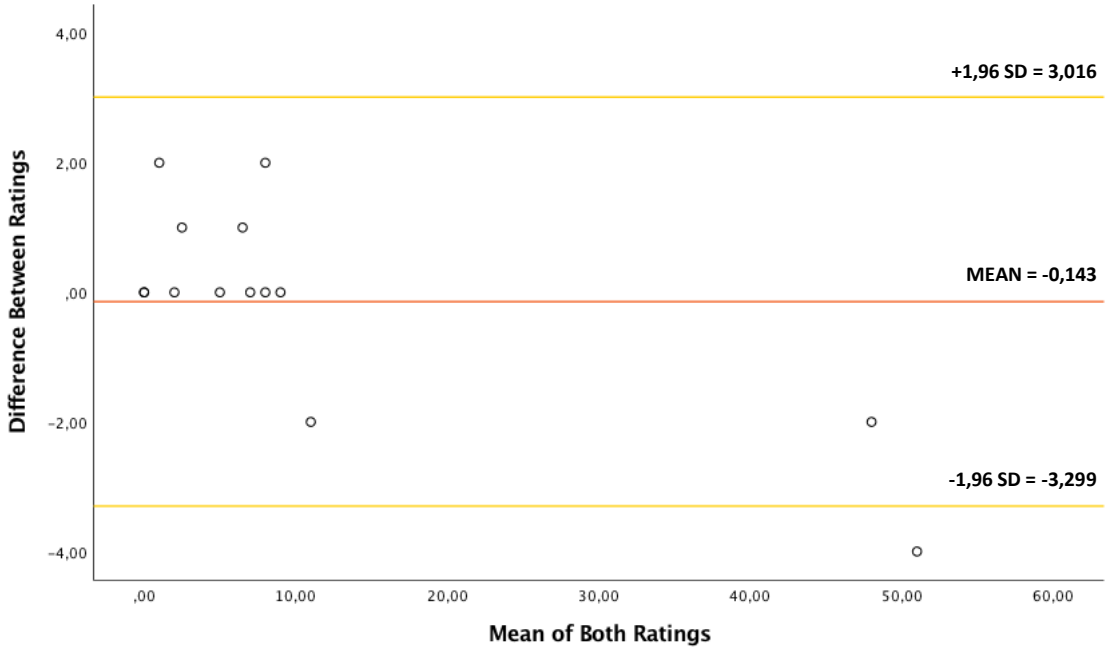


Figure 3 Scatter-plot of observers 1 and 2 total SvdH score at baseline and at 1 year follow-up (PsA)

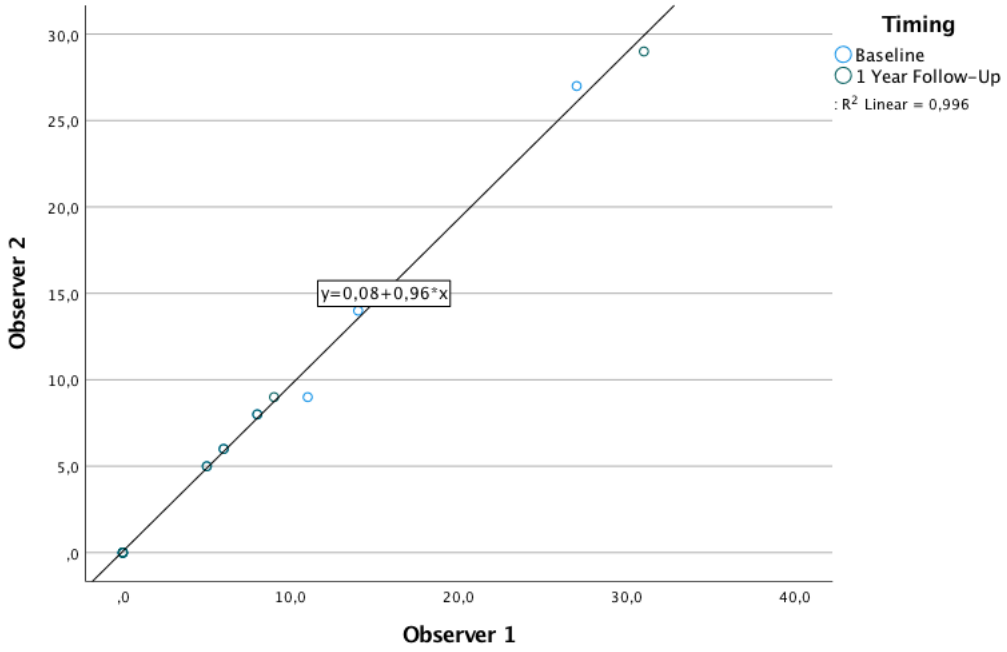


Figure 4 Bland-Altman plot of observers 1 and 2 rating difference t-test (PsA)

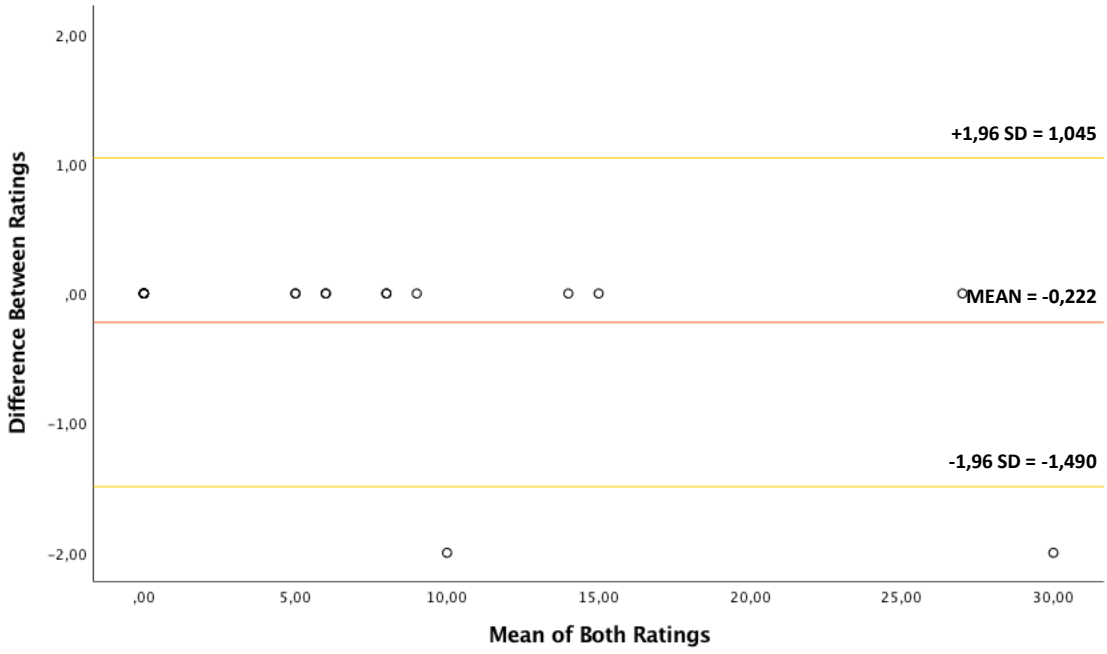


Figure 5 Scatter-plot of observers 1 and 2 total mSASSS at baseline and at 1 year follow-up (axSpA)

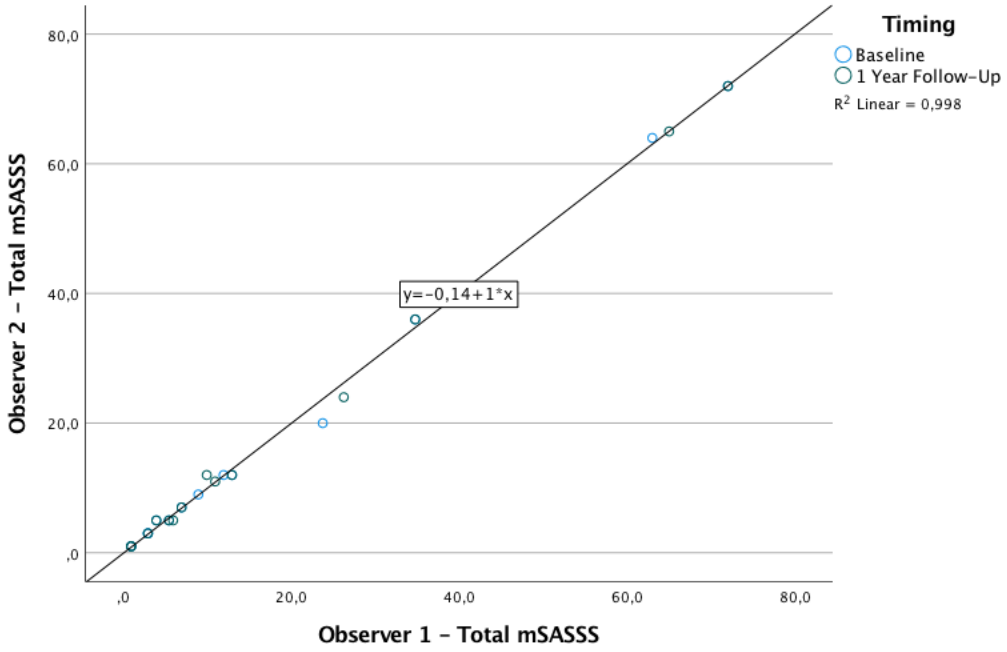


Figure 6 Bland-Altman plot of observers 1 and 2 rating difference t-test (axSpA)