Cervical spine deformity in patients with rheumatoid arthritis: from prevention to prediction

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CHAPTER 1

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which is characterized by progressive articular damage in the small joints of hands and feet as well as in the larger joints. Extra-articular manifestations, such as pulmonary involvement, vasculitis and/or rheumatoid nodules can also exist in these patients.[2] In northern and western Europe, the prevalence of RA is 0.40% with 20-30 new reported cases per 100,000 patient-years. This is comparable to the prevalence of 0.38% and 22.5 per 100,000 patient-years in North America. However, the prevalence of RA is much lower in other continents such as Africa and Asia.[3] Genetic predisposition plays a large role in the development of RA, especially in patients with seropositive disease where the heritability is estimated as 40-65%.[2]

Treatment of rheumatoid arthritis depends on the treatment goals of the patient and has changed quite rapidly over the past decades. Complaints in the acute phase of joint inflammation often comprise of red, swollen and painful joints. These joints will sustain progressive damage during the persistence of inflammation caused by RA. Current treatment goals are often based on the hypothesis that both the acute and chronic consequences of RA are caused by inflammation that causes tissue destruction and loss of function. This would make the aim of treatment simple: control of inflammation. However, even with the vastly increasing number of treatment options, many patients with RA still experience ongoing inflammation and lack of long-term disease control. [4]

Historically, in 1838, the use of concentrated salicylic acid was documented for the treatment of "acute and chronic rheumatism". Later in the 1900s, non-steroidal anti-inflammatory drugs (NSAIDs) were discovered and showed promising results in in vivo models of inflammation, where they reduced complaints caused by inflammation. While NSAIDs still relieve swelling, pain, redness, heat and loss of function in patients with RA, it does not stop the progression of the disease and joint damage.[4]

In 1927, gold salts were observed to be beneficial in the treatment of RA. These effects were confirmed in double blind studies.[5] Unfortunately, gold therapy was not sufficient to control RA in many patients and caused adverse reactions in about 33% of patients. After 5 years, less than 50% of patients continued parental gold therapy, which was attributable to toxicity in 60% of these patients.[6]

Many other drug therapies such as azathioprine and sulfasalazine were researched in the mid-1900s. And in 1987, methotrexate (MTX) was approved by the food and

drug administration (FDA) as a disease-modifying anti-rheumatic drug (DMARD) for the treatment of RA. In the early 2000s, MTX was the most commonly used therapeutic agent in RA.[4] Biological DMARDs, such as infliximab, were introduced in the 1990s and target a specific pathway of the immune system. Initially, these biologicals were prescribed to patients who didn't respond well to conventional DMARDs (often defined by continuously high disease activity or radiographic disease progression). However, it was shown that the use of combination therapy (including biologicals) as initial treatment in patients with early-onset RA causes rapid suppression of inflammation in patients with RA. This is associated with clinical improvement and prevention of radiographic joint damage.[7,8]

In current European guidelines for the treatment of RA, it is advised to start treatment with MTX as soon as the diagnosis of RA is made and treatment should be aimed at reaching low disease activity or sustained remission in every patient. In the initiation of MTX, short-term glucocorticoids should be considered. However, they are advised to be tapered and discontinued as soon as possible to avoid systemic toxicity. If poor prognostic factors are present, such as presence of rheumatoid factor and/or ACPA, presence of early erosions or high swollen joint count, a biological DMARD should be added to treatment if the goal is not reached with the first conventional DMARD therapy.[9]

While the mortality associated with RA has decreased globally over the past decades, the prevalence of RA is rising. The standardized prevalence rate and years lived with disability (YLD) are projected to continue increasing to the year 2050. However, the severity of the disease is generally decreasing, and the mortality associated with RA is declining. Likewise, the consequences of the disease and the disease-associated comorbidities are diminishing.[3] This is probably owed to the more controlled treatment strategies with early diagnosis and immediate treatment with conventional and biological DMARDs.[2] However, it is important to note that not all patients respond to treatment.

The cervical spine

The vertebrae of the cervical spine are stabilized by intervertebral discs, joints and an intricate network of ligaments. Inflammation caused by RA can affect these ligaments and cause laxity, which can lead to instability and subluxation of vertebral bodies. This instability can be present at different levels in de spine. Characteristically, in the cervical spine this consists of atlantoaxial subluxation (AAS), subaxial subluxation (SAS) and in severe cases in vertical translocation (VT). In AAS, there is a subluxation between the C1-C2 vertebra. This can cause pain in the back of the head (occipital neuralgia), caused by compression or at least irritation of the occipital nerve.[10] Due to (intermittent) compression of the medulla, it can also cause weakness in the limbs, tingling and in some cases paralysis. VT is present if there is vertical subluxation of the C2 vertebra. If VT exists, there is a risk of basilar invagination, where there will be compression on the brain stem. In severe cases, this can lead to medullary dysfunction and death. In SAS, there is a subluxation of vertebrae in the subaxial spine (C2-C7; Figure 1).

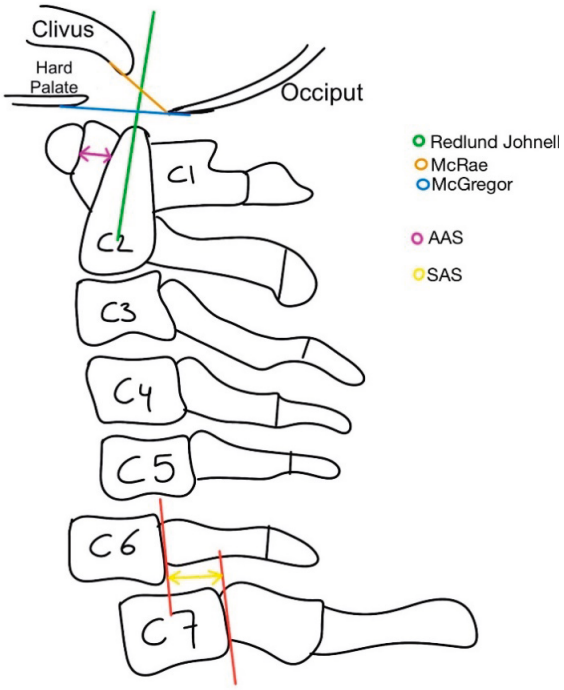

FIGURE 1 - Cervical spine deformity in rheumatoid arthri

Like in AAS, SAS can cause compression of the medulla, which can cause myelopathy, with complaints as described above.[11] It can be challenging to discern the clinical features caused by medullary compression from those caused by the rheumatoid disease itself. For example: rheumatoid arthritis can affect the hands and lead to local deformity, which negatively influences hand function. Disabling hand function can however also be caused by medullary compression. Conventional neurological classifications for motor strength and functioning are therefore less suitable in classifying disease in RA patients. Clinical presentation is thus regularly classified following the Ranawat classification, where patients range between class I (pain without neurological deficit) and class IIIb (objective weakness, long tract signs and nonambulatory).[12]

Surgery to correct cervical rheumatoid arthritis induced deformities is usually indicated when patients experience disabling complaints based on the compression of medulla and/or nerves and/or instability. Surgery usually consists of decompression of the affected level(s) of the spine, followed by fusion to stabilize the instability that exists after decompression in a patient with RA induced laxity of the ligaments. In patients with RA, the bone anatomy is regularly deformed and the bone quality is usually decreased because of the disease. This increases the difficulty of the surgical intervention and makes the patient more prone to complications.[13]

The best trial

The 'BehandelStrategieën' Trial ('Treatment strategies': BeSt Trial) is a randomized, multicenter trial aimed to find the best treatment strategy for patients with early onset RA (newly diagnosed with a symptom duration of less than two years before the initiation of the study). All patients included were 18 years or older with early active RA according to the revised 1987 American College of Rheumatology Criteria for RA.[14] (Figure 2) Patients were recruited between 2000 and 2002 in 18 non-university and 2 university hospitals by Dutch rheumatologists. Patients were randomized in four treatment strategies at baseline, aiming at low disease activity during a 10 year time period.

FIGURE 2: In- and exclusion criteria

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
– Availability of lateral cervical X-ray at 5 years and 10 years of follow-up
– 18 years or older
– Diagnosed with RA; They have active disease with 6 or more swollen joints and 6 or more painful joints and at least one of the following:
1. Westergren erythrocyte sedimentation rate (ESR) of at least 28 mm/hour.
2. Patient's global assessment of general well-being of at least 20 mm measured on a 100 mm horizontal visual analogue scale (VAS).
– Informed consent
A potential subject that meets any of the following criteria will be excluded from participation in this study:
– Previous therapy with DMARDs except for hydroxychloroquine
– Pregnancy or wish to become pregnant during the study, or childbearing potential without adequate contraception
– Concomitant treatment with another experimental drug
– History or presence of malignancy within the last five years
– Bone marrow hypoplasia
– Elevated hepatic enzyme levels (ASAT, ALAT > 3 times normal value)
– Serum creatinine level >150 umol/L or estimated creatinine clearance of <75 mL/ min
– Diabetes mellitus
– Alcohol or drug abuse

The Disease Activity Score (DAS) is a continuous scale to measure disease activity in RA, based on combined information from swollen joints, tender joints, acute phase response and general health. The DAS or DAS44 includes an evaluation of swelling in a total of 44 joints, where the DAS28 is a simplified version of the scale that evaluates 28 joints.[15] Besides its use in clinical trials, the DAS is often used as an indicator of disease activity. In the Netherlands, the DAS is often used in clinical practice as an indicator of treatment effect. In the BeSt Trial, low disease activity was defined as a disease activity score (DAS) ≤ 2.4. Remission was defined as a DAS < 1.6 and after at least 6 consecutive months of remission, a patient was defined to be in sustained remission.

As mentioned, the BeSt Trial compares four treatment strategies. In the first treatment strategy patients received sequential monotherapy, starting with methotrexate and continuing with sequential DMARD monotherapy in each consecutive step. In the fourth step of this treatment infliximab is added to MTX therapy. In strategy two, patients received step-up combination therapy starting with methotrexate monotherapy and adding medication (such as sulphasalazine, prednisolone and/or infliximab) in

each step. In strategy three, patients received initial combination therapy with methotrexate, sulfasalazine and prednisone. In this strategy, the step up design consisted of changing medication for infliximab, for example. Lastly, in strategy four, patients received initial combination therapy with methotrexate and infliximab.

During the 10 follow up period, patients disease activity was monitored every 3 months using the disease activity score (DAS). This score is based on a swollen joint count in 44 joints, a tender joint count in 53 joints, erythrocyte sedimentation rate and the patient's assessment of global health on a visual analog scale (0 to 100 mm).[16] Clinical outcomes were measured using the Health Assessment Questionnaire (HAQ). Also, cervical spine X-rays were taken at 5-year and 10-year follow-up for most patients and X-rays of the hands and feet were assessed for the Sharp-van der Heijde score (SHS) every year.[8]

Depending on the patients' response in DAS, treatment adjustments within the strategy-arm they were randomized to, were made. Treatment was intensified if the DAS was higher than 2.4 (high disease activity) and tapered if the DAS was 2.4 or lower for at least 6 months. If a patient's DAS remained below 1.6 for at least 6 months (sustained remission) medication was stopped (drug-free remission). If the DAS increased above 1.6 again after sustained remission, medication was started again. Treatment adherence in BeSt was high at 87%.[17]

The use of artificial intelligence

The use of artificial intelligence has vastly increased in medical literature over the past years. Artificial intelligence is a broad term that includes every technology that simulates human intelligence and problem-solving capabilities.[18] The words artificial intelligence, machine learning and deep learning are often used interchangeably, while machine learning and deep learning are actually subsets of artificial intelligence. (Figure 3) In machine learning, data and algorithms enable AI to learn and improve its accuracy for a task. In deep learning, this is accomplished with the use of deep neural networks, which simulate the architecture of the human brain. This can be compared to the layers of an onion, where the first layer might start with simple things such as shapes and colors. The second layer will look at combinations of the aspects observed in the first layers and the deeper layers of the onion can understand more and more complicated things such as sounds, objects and faces.

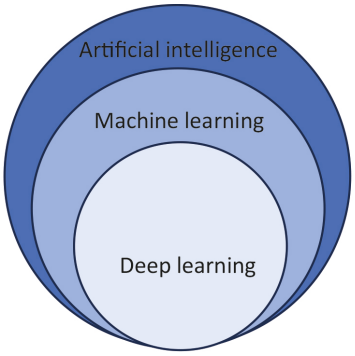

FIGURE 3 - Artificial intelligence

This can be further specified in supervised learning, where a specific labeled input is used to predict a predefined output. In supervised learning, the data will be split in a training and a testing set. The training consists of the system looking for patterns in the input it was given, such as the feathers and beaks of birds in an input of birds versus not birds. The system will over time become good at discerning birds from everything else. In unsupervised learning, raw data can be used as input and the model will find structure in the data by itself.

Many things we use on a daily basis use artificial intelligence. Cars for example, use AI to understand their surroundings and make decisions to be able to drive autonomously.

While conventional statistics such as a logistic regression can also be used to analyze the relationship between input and output (or exposure and outcome), machine learning can handle a large set of data with many variables and determine complex interactions. However, machine learning models are often harder to interpret and therefore harder to implement in medical practice.[19] These models are often seen as a 'black box', since humans cannot understand the decisions made by the models. This makes it hard for medical professionals to use AI in clinical practice, while the role of AI in healthcare is rapidly evolving, for example to detect early signs of disease on medical imaging and in the prediction of health risks.

In this thesis, conventional statistics as well as artificial intelligence have been used in order to visualize and analyze data. The artificial intelligence tool 'segmentation

modelling' is used in this thesis, as well as 'deep learning'. Segmentation modelling, among other designs, includes the division of a medical image in distinct regions – or 'segments' – meaningful for analysis. In deep learning neural networks are used to study and learn patterns in large sets of data, such as imaging. Deep learning can be used for diagnosis and treatment planning, but also in prediction of a future outcome based on large sets of imaging data.

Aims and outline of this thesis

In current practice, it seems that the number of surgeries for severe RA-associated deformity is declining.[20] It has been hypothesized that cervical spine RA associated deformities like AAS, SAS and VT rarely exist in the Western world with the introduction of the improvement of treatment methods for patients with RA. However, these deformities do still exist and it is currently unknown which patients with RA are at risk of developing cervical spine deformity. This thesis aims to study ways to prevent and predict RA associated cervical spine deformity in patients with RA.

In C*hapter 2*, a systematic overview is given of the available literature on the association between systemic disease activity (DAS) and cervical spine deformity. This overview is important to provide, since DAS is often used as an indicator of treatment response in rheumatoid arthritis in many countries, including the Netherlands. The use of DAS as an indicator for disease activity in joints of hands, wrists, and for general health and survival have previously been reported extensively[21], while the correlation between DAS and cervical spine deformity was only highlighted scarcely in literature.

Since literature did not provide a satisfactory answer to the previously described questions, the data from the BeSt Trial were evaluated for the correlation between DAS and cervical spine deformity. The available X-rays of the cervical spine that were made after 5 and 10 year were scored for RA-associated cervical spine deformities: AAS, SAS and VT. *Chapter 3* describes the association between (mean) disease activity score and RA-associated cervical spine deformity in the patients of the BeSt Trial.

As described in the outline of the medical treatment regimens of the BeSt Trial, patients can have a 'flare' of disease after the disease seemed adequately treated: this means that the inflammation 'flares up' reflected by an increase in DAS. In *Chapter 4*

the association of the number of flares in DAS with the presence of RA associated cervical spine deformity is evaluated. The association of DAS with flares was studied separately, since we hypothesized that cervical spine deformity might be present more often in patients who experienced many flares in disease activity.

Another aim of this thesis was to identify the effect of the medication used by patients in the BeSt Trial. *Chapter 5* describes the influence of glucocorticoid use. Glucocorticoids have an anti-inflammatory effect, which is beneficial to decrease the inflammation in RA. However, glucocorticoids are also known to have a detrimental effect on bone and it was hypothesized to have a negative effect on the cervical spine anatomy. In *Chapter 6* the use of infliximab is evaluated for its influence on cervical spine deformity. Infliximab use has been described in literature to prevent joint damage in hands and feet regardless of DAS.[22] We therefore hypothesized that infliximab might also have a protective effect in RA induced cervical deformity regardless of DAS.

An important step in prevention, is early recognition. Since the assessment of X-rays of the cervical spine takes extensive time of a person trained to study these images, it would be very costly and time-intensive to screen patients with RA for the presence of cervical spine deformity. In order to take a next step towards this possibility and to be able to speed up the imaging assessment of future research an automated segmentation model for the upper cervical spine was developed. In *chapter 7* of this thesis, the development and internal validation of such a segmentation model is described.

Lastly, to go from prevention to prediction, a deep learning study was performed to predict development of RA associated cervical spine deformity in patients with RA close to – or before – diagnosis based on MRI imaging of the cervical spine of patients in the United States. This is described in *Chapter 8*.

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