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Saint James: Reflections on a Long Road of Treatments from Rheumatoid Arthritis to COVID-19

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Abstract

For centuries, Santiago de Compostella has been the destination of pilgrims to visit the grave of Saint James. Saint James himself, patron Saint for arthritis and rheumatism, is depicted on one of the back panels of The Last Judgement by Jheronymus Bosch. Rheumatoid arthritis is a relative common chronic inflammatory joint disease, for which there is no cure available. Treatment is aimed to limit progression of the disease and pain relief. While in the past steroid and non-steroidal anti-inflammatory drugs were mainly used, over the last decades (biological) disease modifying antirheumatic drugs have been successfully implemented. Some antirheumatics drugs have been repurposed for treatment of severe COVID-19.

Introduction

The Last Judgement is a painting of Jheronymus Bosch which was completed around 1506 and is currently on display in the Academie der bildenden Künste in Vienna, Austria. The left back panel of this painting shows Saint James, bare footed, wearing a long robe, holding his walking stick and the characteristic pilgrim's hat with the St. James' scallop (Figure 1). The St. James' scallop in the painting is a clear anachronism because Saint James certainly was not on a pilgrimage to his own grave. The St. James' scallop is used often by pilgrims on route towards Santiago de Compostella (Sant Iago is Saint James in Spanish), assuming that over there Saint James has been buried. The scallop was more than a symbol, it also served as a lightweight food plate for on the road. The ration you could get in churches and stopping places along the route was tailored to it. The scallop is also used as an ornament on all buildings along the pilgrimage routes that run into the city from all directions. There are many different routes that pilgrims can choose to eventually reach Santiago de Compostella [1]. From the North, there are several options that converge in the Camino Frances. From Portugal you can take the Camino Portugues and from within Spain there are several routes such as the Camino Catalan and the Via de la Plata.

Santiago de Compostella may have been a pilgrimage site long before Saint James died in the year 44 AC, and then of course for other reasons. The scallop also is a symbol for fertility and birth, but in those instances displayed with the concave interior surface (cf. the Venus of Botticelli).. Saint James is the patron Saint for pilgrims and also for travelers in general. For the latter patronage Saint James is in competition with Saint Christopher [2]. Saint James is also called upon for a number of diseases, but in particular arthritis and rheumatism [3]. Rheumatism, Rheumatoid Arthritis (RA), is a chronic, symmetrical, inflammatory autoimmune disease that starts in small joints, progresses to larger joints, and eventually the skin, eyes, heart, kidneys and lungs [4]. Over the course of the disease, joint bone and cartilage is destroyed, leading to deformities and erosion of the bone, which makes movement cumbersome and very painful. Common symptoms include morning stiffness for more than 30 minutes, fatigue, fever, weight loss, tender, swollen and warm joints, and rheumatoid nodules under the skin [5]. The onset of the disease usually is between the age of 35 to 60 years, is accompanied by periods of flare-up and remission, and occurs in 1 to 2% of the population [6].

Treatment of Rheumatoid Arthritis

There is no cure for RA, treatment for RA aims to reduce joint inflammation and pain, maintain joint function and prevent joint destruction and deformity [7,8]. The initial treatment of RA is with corticosteroids, because they provide a rapid control of disease activity in the early stages, and they serve as a bridge between the

start of treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and the onset of action. DMARDs show only a first effect after weeks, or even months. After initial treatment, RA is treated with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin and ibuprofen. In this context it is relevant to point out that aspirin as pain relief medication has a history of over 3000 years [9]. Clay tablets from the Assyrians during the Sumerian period already have the recipe to prepare such a medicine from willow bark [10]. The Catholic church, based on the argument that man is created after the image of God and thus should be perfect, for centuries opposed research into pharmacological treatment of chronic diseases [11]. Christians therefore had to rely on the placebo effect of hagiotherapy and calling upon the help of patron Saints, such as Saint James. When NSAIDs are insufficiently effective, a switch is made to the next category of drugs, the DMARDs: disease-modifying anti-rheumatic drugs. This category includes agents such as methotrexate, leflunomide, hydroxychloroquine (for milder forms of RA) and sulfasalazine, as an alternative for methotrexate [12,13]. Methotrexate is an effective drug in about 40% of patients [13]. In their review on the mechanisms of action of methotrexate in rheumatoid arthritis from 2106, Brown et al. conclude that "despite a long history of clinical application and demonstrable efficacy in RA, the precise mechanism by which low-dose methotrexate provides therapeutic benefit remains incompletely understood" [13]. All of the above agents can have serious side effects, but if the disease does not go into remission, azathioprine (Imuran), cyclophosphamide and cyclosporine can be used [14].

Figure 1: Saint James painted on the left back panel of The Last Judgement. Jheronymus Bosch, ca 1506, Academie der bildenden Künste, Vienna, Austria. https://commons.wikimedia.org/wiki/File:Jheronimus_Bosch_Last_Judgment_triptych_(Vienna)_exterior.jpg Assessed January 26, 2021.

A separate category of drugs are the biological DMARDs which are targeted and very effective in slowing the progression of the disease [15]. This category includes Tumor Necrosis Factor (TNF) inhibitors such as etanercept (Enbrel) [16], infliximab (Remicade) [17] and adalimumab (Humira) [18]. Anakinra is an IL-1 receptor antagonists and blocks another major proinflammatory cytokine IL-1 [19]. For patients refractory to methotrexate and TNF inhibition, Tocilizumab, a blocking IL-6 receptor antibody, is an alternative [20,21]. If the above agents are not effective (enough), rituximab (Rituxan) can be used, an antibody directed against the CD20 molecule on B lymphocytes [22]. Abatacept is another biological DMARD that works by blocking the activation of T lymphocytes [23]. Abatacept binds CD80/CD86 on antigen presenting cells, thus preventing costimulatory binding of CD28 on T lymphocytes. When this drug was released in 2007, Heather Won Tesoriero, a journalist for The Wall Street Journal wrote: "The last time a new drug was approved to treat lupus, a serious autoimmune disorder that afflicts an estimated 1.5 million Americans, Dwight D Eisenhower was president. " [24] In the same year the last drug was approved, Elvis Presly bought Graceland for $100,000, John Lennon met Paul McCartney, and Laika became the first dog in space. Fifty years later it really was time for new drugs for serious autoimmune diseases such as RA and lupus.

The most recent route that has been constructed and that can be taken for relief of rheumatoid arthritis is built on drugs that can inhibit a specific tyrosine kinase called JAK. This is the category of targeted synthetic DMARDs (tsDMARDs). These drugs carry names like tofacitinib [25], baricitinib [18], and upadacitinib [26]. How quickly this route will lead to the final goal is not yet known. GS-9876, a tsDMARD targeted at another tyrosine kinase, SYK, is currently under investigation for use in autoimmune diseases including RA [27]. As with a pilgrimage, the treatment of rheumatoid arthritis can take different routes to reach ultimately the same goal. Different routes can converge at some point, in the form of combination therapy. It is remarkable, however, that the various bDMARDs, with different modes of action show similar clinical efficacy [28].

Repurposing of anti-inflammatory rheumatoid arthritis drugs for treatment of COVID-19

Many of the drugs described above act by a general or targeted inhibition of the inflammatory processes in RA. Severe COVID-19 also is characterized by a massive inflammatory response [29,30]. High levels of IL-6 and TNF-α have been found in COVID-19 patients who required intensive-care hospitalization [31]. This provided the rationale repurposing of (anti-inflammatory) rheumatic arthritis drugs as potential treatment for severe COVID-19 [31]. A great number of anti-inflamatory rheumatoid arthritis drugs indeed have been investigated for

treatment of COVID-19 [32]. The data, summarized in Table 1 show that the IL-1 receptor anatagonist Anakinra [32,33], the IL-6 receptor blocking antibody Toculizumab [34,35] and the tyrosine kinase inhibitor Baracitinib [36,37] can induce clinical improvement in severe cases of COVID-19 and/or limit the progression to the severe phenotype of the disease. These drugs limit the consequences of the cytokine release storm in severe COVID-19 by blocking the relevant cytokine receptors (Anakinra and Toculizumab) or the signaling pathways of these receptors (Baracitinib). Unfortunately, and despite 2261 publications on the subject on PubMed (February 8, 2021), hydroxychloroquine turned out to be ineffective [38,39]. It should be kept in mind that none of these drugs, nor any other drug used for treatment of RA, is an anti-viral. Therefore, the best possible effect is reducing the immunopathology of an overactive inflammatory response. In this respect it is surprising that TNF blockade, as a potential form of treatment for COVID-19, has not yet been widely studied [40-42]. Observational data in the form of small case series show potential benefit of anti-TNF therapy. Data from large registries of patients with immune-mediated inflammatory diseases have demonstrated an inverse association of anti-TNF use and outcome of COVID-19 [43-45]. Randomized, placebo controlled clinical trials on the effect of TNF blockade on COVID-19 (such as the CATALYST trial; https://www.isrctn.com/ISRCTN40580903) are underway and the outcomes are eagerly awaited.

Drug	Category RA treatment	Effective in COVID-19	COVID-19 outcome in RA patients
Aspirin	NSAID	May be associated with improved outcomes in hospitalized patients [46]	
		Reduces thrombosis and pulmonary embolism related mortality [47]	
Ibuprofen	NSAID	No negative effects [48]	No effect [49]
Hydroxychloroquine	csDMARD		
		Does not improve clinical outcome of COVID-19 [38]	No increased risk of getting COVID-19 [50]
		Ineffective as post-exposure prophylaxis [39]	
Methotrexate	csDMARD	Suggested [51]	No effect [52]
Sulfosalazine	csDMARD		Associated with severe COVID-19 in IBD patients [43]
Azathioprine (Imuran),			No effect [53]
Cyclophosphamide			Unknown because mostly used in combination therapy
Cyclosporine		No robust clinical data [54]	Caution [55]
TNF blockade (Etanercept, Adalimumab, Infliximab)	bDMARD	Suggested [40-42]	No effect [52]
Il-1 receptor antagonist (Anakinra)	bDMARD	Beneficial for severe Covid-19 patients with Secondary HLH[32]	
		Reduced both need for invasive mechanical ventilation in the ICU and mortality [33]	
Rituximab (anti-CD20)	bDMARD		Adverse clinical outcome [56]

Abatacept (anti-CD80/86)	bDMARD	Not studied	Unknown
Tocilizumab (IL-6)	bDMARD	not effective for preventing intubation or death in moderately ill hospitalized patients [34]	
		improves the clinical outcome in severe and critical patients [35]	
Ustekinumab (IL-12/23)	bDMARD		Relative protection of severe COVID-19 [57]
Tofacitinib	tsDMARD	Suggested [58]	
Baracitinib	tsDMARD	Suggested [58,59]	
		Reduces morbidity and ICU admission in small open label study [36]	
		Reduces time to recovery when combined with Remdesivir [37]	
Upadacitinib	tsDMARD		Potential risk [58]

DMARD: Disease Modifying Anti-Rheumatic Drug; cs: Conventional Synthetic; ts: Targeted Synthetic; b: biological; HLH: Hemophagocytic Lymphohistiocytosis

Table 1: Clinical effects of rheumatoid arthritis drugs on COVID-19.

Rheumatoid arthritis in times of corona

Patients with RA are immunocompromised, both because of their autoimmune disease and of the immunosuppressive medication. Whether that would mean that they are at a higher risk of severe COVID-19 is not clear. Indeed, the immune response to SARS-CoV-2 infection can be impaired, but, on the other hand, immunosuppressive drugs, such as the ones indicated above, may limit the harmful effects of hyperinflammation. Apart from Anakinra, Tocilizumab, and Baracitinib, RA patients also may benefit from the IL-12/23 antibody Ustekinumab [57]. On the other hand, the anti-CD20 antibody Rituximab has been associated with a more severe clinical course of COVID-19 [56]. For Cyclosporin [55] and the tyrosine kinase inhibitor Upadacitinib [58] the limited available data indicate that care should be taken. The clinical care for patients with chronic diseases, including rheumatic diseases, has come under pressure during the COVID-19 pandemic [60]. Because of the reduction of in hospital face-to-face contacts, patients on intravenous abatacept or tocilizumab have been asked to switch to subcutaneous (self) administration. Many patients are reluctant to do so, and the outcome is not always favorable [61,62]. In order to address these and other issues, the Global Rheumatology Community's Response to the Worldwide COVID-19 Pandemic (rheum-covid.org) have created a web-portal with the aim to "collect, analyze, and disseminate information about COVID-19 and rheumatology to patients, physicians and other relevant groups to improve the care of patients with rheumatic diseases". Currently (February 8, 2021), 10,557 global cases have been reported and included.

As a side effect of the COVID-19 pandemic and the need for effective drugs, the interest of the general public for the implications and risks of anti-rheumatic drugs has changed. Significant increase of relative search volumes on the internet were found for hydroxychloroquine, tocilizumab and anakinra, but a decrease in search for azathioprine, cyclophosphamide and cyclosporine. Search volumes for hydroxychloroquine went up especially after the endorsement of Egon Musk and Donald Trump for the use of this drug [63,64]. Apart from the risks of SARS-CoV-2 infections, the treatment of RA is not without side effects, sometimes even life-threatening. Infections with intracellular growing micro-organisms such as *Mycobacterium tuberculosis* in particular are feared side effects of anti-TNF therapy [65-67]. Because activation of latent tuberculosis can occur, a positive skin test for *M. tuberculosis* or an in vitro quantiferon assay is a contra-indication for anti-TNF [68]. Other infectious complications of anti-TNF therapy should be carefully controlled but, fortunately, are limited [69-71].

Patron Saints for rheumatism

It is remarkable that in the Bosch's painting of Saint James, no direct reference is made to the miracle by which he became the patron Saint for arthritis and rheumatism. The legend goes that on the way to his own execution, Saint James passed a man, a beggar, crippled by arthritis. He cured the man of his disease, under the condition that he would convert to Christianity. The left border of the panel with Saint James shows four scenes that maybe have a connection with the burden of arthritis: behind James a hooded crow is sitting in a dead tree, which could be interpreted as a warning of illness and death? (Figure 2, panel a). Panel b of figure 2 shows two pilgrims holding each other, one cripple (due to rheumatism?) and the other one blind. In panel c, a pilgrim is at rest, but in panel d on the very top of a rock a pilgrim has hung himself or is the victim of a brutal assault. The route of the pilgrimage to the grave of Saint James was not and is not without danger. All in all, at best indirect references to rheumatism.

The portrait of Saint James is painted on the left back panel of The Final Judgement. The right back panel is painted with a portrait of Saint Bavo. Saint Bavo also is a patron Saint for protection against a number of diseases, in particular lung and throat diseases, including whooping cough but certainly not arthritis. At the feet of Saint Bavo, a beggar with clear signs of deformations of his hands is sitting against the wall (Figure 3). The meaning of the cut-off foot on display in front of him is unclear [72]. It might be Jheronymus Bosch has mixed up the patronages of both these Saints.

Figure 2: Details of the Saint James panel. Jheronymus Bosch, ca 1506, Academie der bildenden Künste, Vienna, Austria. https://commons.wikimedia.org/wiki/File:Jheronimus_Bosch_Last_Judgment_triptych_(Vienna)_exterior.jpg Assessed January 26, 2021.

Figure 3: Detail of Saint Bavo painted on the right back panel of The Last Judgement. Jheronymus Bosch, ca 1506, Academie der bildenden Künste, Vienna, Austria. https://commons.wikimedia.org/wiki/File:Jheronimus_Bosch_Last_Judgment_triptych_(Vienna)_exterior.jpg Assessed January 26, 2021.

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