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Immunomodulatory and immunosuppressive therapies in cardiovascular disease and type 2 diabetes mellitus: A bedside-to-bench approach

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A B S T R A C T

Objective: To assess which immunosuppressive drugs have been investigated and proven efficacious in patients with cardiovascular disease (CVD) or type 2 diabetes (T2D) without preexisting immune mediated disorders to validate in vitro and animal model findings on low grade inflammation (bedside-to-bench).
Methods: Clinical trials on immunosuppressive drugs in CVD or T2D were found in PubMed. Studies on patients with preexisting immune mediated inflammatory disease were excluded. A total of 19 clinical trials testing canakinumab, anakinra, methotrexate, colchicine, hydroxychloroquine, etanercept and sulfasalazine were found.
Results: Canakinumab and colchicine significantly reduced the risk of CVD, whereas methotrexate did not. Sulfasalazine showed no effect on vascular function. Anakinra and hydroxychloroquine had a positive effect on glycemic control and β-cell function in T2D. Etanercept had no effect in patients with T2D.
Conclusion: The observed results indicate that immunosuppressive drugs specifically targeting IL-1β hold promise for dampening CVD and T2D. These findings validate in vitro and animal models showing involvement of the IL-1-axis in the pathogenesis of CVD and T2D. The use of immunosuppressive drugs targeting the chronic inflammation in these diseases could be a possible future treatment strategy as an add-on to the existing pharmacological treatment of CVD and T2D. However, potential treatment effects, adverse events and cost-effectiveness should be carefully considered with importance for drug development.

1. Introduction

1.1. Cardiovascular disease and type 2 diabetes

1.1.1. Prevalence and prognosis

Cardiovascular disease (CVD) or type 2 diabetes (T2D) are both associated with metabolic derangement and a state of low-grade inflammation; hence it is relevant to investigate the immunological aspects of these diseases together. Worldwide, CVD is highly prevalent and especially myocardial infarction (MI) and stroke are both potentially fatal outcomes. According to the World Health Organization (WHO), 31% of all deaths worldwide were caused by CVD in 2016 (World Health Organization, 2017), making it the most frequent cause of death globally. Although not as prevalent, it was estimated in 2018 that more than 500 million people worldwide suffer from T2D, with an increasing prevalence (KAISER et al., 2018). In addition to the strong relationship between T2D and development of CVD (i.e. MI and stroke), other long-term and severe consequences of T2D such as kidney failure, blindness, and amputation are well-known (World Health Organization, 2020). Thus, both CVD and T2D are frequent disease entities with severe consequences even with treatment of conventional risk factors, why new treatment modalities are needed.

1.1.2. Inflammation

There is growing evidence that low-grade inflammation plays a pathophysiological role in the development of diseases such as CVD and T2D (Ouchi et al., 2011).

Atherosclerosis is an important pathological substrate in CVD and can be considered as a chronic inflammatory condition dominated by monocyte-derived macrophages and T-cells. For instance, macrophages are activated by modified LDL, e.g. oxidized LDL, leading to an increased production of proinflammatory cytokines (e.g. IL-6, IL-1β and TNFα), chemokines and growth factors (Hajjar and Haberland, 1997).

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List of abbreviations

CI	Confidence interval
Hs-CRP	High-sensitivity C-reactive protein
CVD	Cardiovascular diseases
DMARD	Disease-modifying anti-rheumatic drug
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
HbA_{1c}	Hemoglobin A_{1c}
HCQ	Hydroxychloroquine
HR	Hazard ratio
IL	Interleukin
MTX	Methotrexate
NFκB	Nuclear factor kappa B
NOX2	Endosomal NADPH oxidase 2
PIO	pioglitazone
RCT	Randomized-controlled trials
SD	Standard deviation
SLR	systematic literature search
TLR	Toll-like receptors
TNFα	Tumor necrosis factor alpha
TGF-β	Transforming growth factor beta
T2D	Type 2 diabetes

Furthermore, cholesterol crystals have shown to trigger the NLRP3 inflammasome, resulting in release of active IL-1β (Nidorf et al., 2014). T-cells are also activated by antigens in the vessel wall as well as through an interaction with macrophages, consequently enhancing the local inflammatory activity, resulting in a progression of plaque formation (Golia et al., 2014). One of the key inflammatory proteins, C-Reactive Protein (CRP), is a significant risk factor for cardiovascular events, contributing to atherosclerotic progression and ultimately acute coronary events. CRP can directly increase the inflammatory activity in the atherosclerotic plaque, and it seems to be associated with a destabilization of the plaque by increasing the synthesis of metalloproteinases (MMP), leading to matrix degradation and plaque instability. Also, CRP seems to induce an increased expression of tissue factor in endothelial and smooth muscle cells, and it inhibits fibrinolysis (Bisoendial et al., 2007), thus increasing the risk of intravascular thrombus formation if the plaque ruptures.

In T2D, increased level of acute-phase proteins (e.g. high-sensitive (hs)-CRP) and proinflammatory cytokines (e.g. IL-1β and IL-6) have been found (Donath and Shoelson, 2011; Herder et al., 2005). IL-1β-induced inflammation is thought to contribute to the development of β-cell dysfunction and in addition to inflammatory stimuli, IL-1β can be activated by high levels of glucose and free fatty acids, respectively (Zhou et al., 2010). Additionally, an increased number of intra-islet macrophages are seen in patients with diabetes, which is a direct source of IL-1β due to autocrine stimulation (Mandrup-Poulsen, 2013). Both glucose and IL-1β upregulate the expression of the pro-apoptotic Fas receptor in β-cells, suggesting that IL-1β is a part of the pathogenesis of glucotoxicity in T2D (Donath and Shoelson, 2011).

The fact that CVD and T2D are related to chronic low-grade inflammation suggests that targeting these diseases with immunomodulating medication could be considered a future type of treatment. Contributing to this concept is the fact, that use of certain disease-modifying anti-rheumatic drugs (DMARDs) already has shown positive effects on both diseases when used in patients with rheumatoid arthritis (Atzeni et al., 2021b; Micha et al., 2011; Stagakis et al., 2012) as well as suppressing effects on cardiovascular risk in patients with psoriatic arthritis (Atzeni et al., 2021a).

1.2. Immunosuppressive drugs

1.2.1. Drug classes

DMARDs comprise several immunosuppressive drugs used to treat immune mediated inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. This drug class is most often grouped in 1) conventional synthetic drugs, 2) targeted synthetic drugs, and 3) biologic drugs. This nomenclature differentiates between drugs originally designed for the treatment of other diseases such as cancer and malaria (conventional synthetic drugs), and drugs with a well-described immunological target identified before the development of the drug (targeted synthetic and biologic drugs) (Smolen et al., 2014).

1.2.2. Specific DMARDs

Knowledge about the pharmacodynamics and current approved indications of the DMARDs can assist the interpretation of the results from the clinical trials identified in this systematic literature review (SLR). Table 1 summarizes the currently approved indications of the DMARDs included in this study.

Canakinumab (humanized monoclonal antibody against IL-1β) and anakinra (IL-1 receptor antagonist) act by inhibiting IL-1β (Fig. 1). Canakinumab and anakinra are approved for the treatment of several periodic fever syndromes and Still's disease. Additionally, anakinra can be used to treat rheumatoid arthritis. However, IL-1β inhibition in rheumatoid arthritis has shown only modest efficacy. In the immune system, IL-1β is primarily secreted by macrophages and neutrophilic granulocytes and is mostly associated with functions of the innate immune response. IL-1β secretion is induced by an activation of caspases and the formation of the NLRP3 inflammasome. IL-1β signals via the Toll/interleukin-1 receptor (TIR) homology domain and the adaptor protein Myeloid differentiation primary response 88 (MyD88). MyD88 triggers a cascade of kinases that produce a pro-inflammatory signal leading to the activation of NFκB and production of proinflammatory cytokines (Malcova et al., 2020).

MTX is an antimetabolite chemotherapeutic with anti-inflammatory properties when used in lower doses. MTX is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and psoriasis, but is also used for several other immune mediated inflammatory diseases including vasculitis and connective tissue diseases. Because the pharmacodynamics of MTX are poorly understood, the immunological understanding of MTX is more difficult. MTX inhibits the de novo synthesis of purines and pyrimidines. This suppresses highly proliferating cells such as T cells in inflammatory arthritis. However, other proposed mechanisms include enhanced adenosine release, inhibition of transmethylation reactions that are required for some cellular functions, diminished accumulation of polyamines and nitric oxide synthase uncoupling. Taken together, MTX is hypothesized to primarily mediate suppression of T cell proliferation and macrophages differentiation and activation (Cronstein and Aune, 2020).

Colchicine is an anti-inflammatory compound. The plant source of colchicine was used in ancient Egypt to treat inflammatory conditions. Colchicine is today approved for the treatment of acute gout flares and in the management of familial Mediterranean fever. Colchicine inhibits the assembly of the NLRP3 inflammasome reducing the release of active IL-1β (Fig. 1). However, colchicine also impedes motility and adhesion of neutrophils and reduces the effects of T cells and mast cells. Furthermore, it causes macrophages to release anti-inflammatory cytokines such as IL-10 and TGFβ (Leung et al., 2015).

HCQ is an antimalarial drug. In the treatment of systemic inflammatory diseases, HCQ is approved for systemic lupus erythematosus and rheumatoid arthritis. HCQ inhibits the function of lysosomes, preventing the binding of ligands to the intracellular TLR 3, 7 and 9. This will inhibit inflammation, as these innate immune receptors are activated by

Table 1
Overview of selected approved indications for the DMARDs included in this study.

	Rheumatoid arthritis	Psoriasis	Systemic lupus erythematosus	Periodic fever syndromes	Still's disease	Gout attacks
IL-1-inhibitor						
Methotrexate						
Colchicine						
Hydroxychloroquine						
TNF-inhibitor						
Sulfasalazine						

Approved indication *Not approved indication*

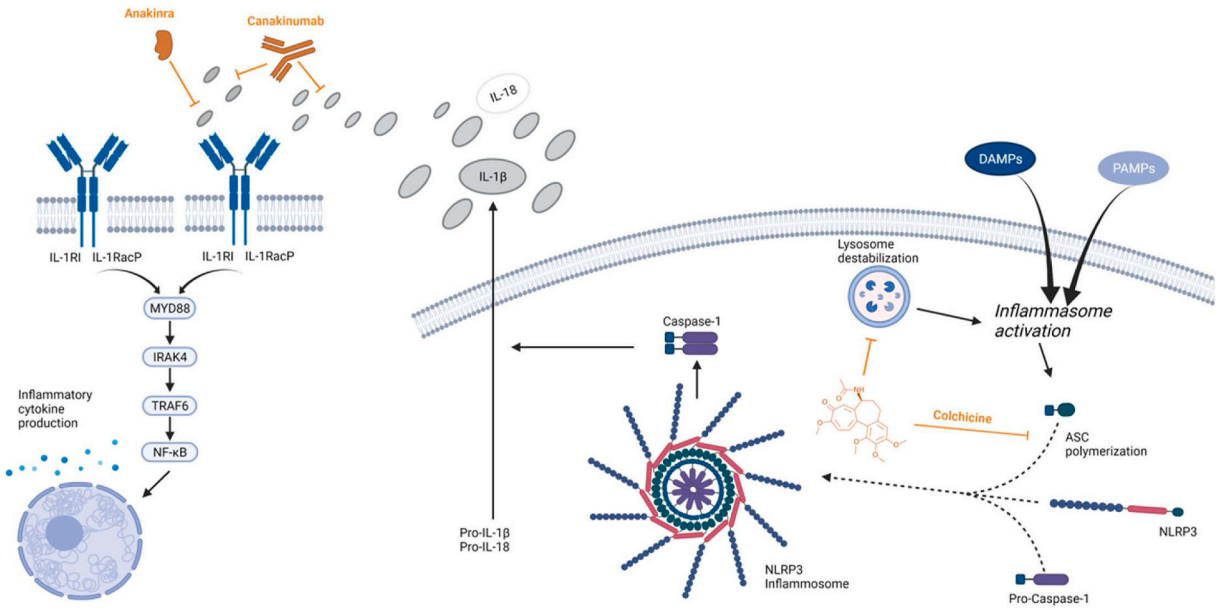

Fig. 1. Molecular targets of immunosuppressive drugs interfering with the IL-1β system. Colchicine inhibits activation of the inflammasome and therefore prevents secretion of active IL-1β. Canakinumab and anakinra prevent binding of IL-1β to the IL-1 receptors. Created with BioRender.com.

DAMPs and PAMPs. Additionally, HCQ can inhibit adaptive immunity if accumulated in antigen-presenting cells (Ponticelli and Moroni, 2017). Furthermore, HCQ has shown to prevent the induction of IL-1β and TNFα by inhibiting NOX2 (Müller-Calleja et al., 2017; Schrezenmeier and Dörner, 2020).

Etanercept is a soluble TNFα receptor fusion protein acting by inhibiting TNFα. It is approved for the treatment of several immune mediated inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, and inflammatory bowel disease. The TNFα-inhibitor etanercept binds to circulating TNFα and lymphotoxin-α (Sedger and McDermott, 2014).

Sulfasalazine is an anti-inflammatory drug. It is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and ulcerative colitis. The immunomodulatory effects of sulfasalazine and its metabolites is not clear, but it has been shown to inhibit the transcription factor NFκB and thereby suppress the production of TNFα. It also inhibits the expression of TNFα by inducing apoptosis in macrophages. Other suggested effects are inhibition of B-cell function and suppression of the production of IgM and IgG, enhanced adenosine release and inhibition of leukocyte accumulation (Choi and Fenando, 2021).

1.3. The "reverse translational" or "bedside-to-bench" concept

Clinical trials with immunosuppressive drugs can help confirm or disprove hypotheses based on in vitro and animal model findings (Brüner et al., 2021; Schett et al., 2013; Torp et al., 2021). For instance, IL-17-inhibition has shown a positive effect on psoriasis but not rheumatoid arthritis, indicating that IL-17 plays a more significant role in psoriasis. Contrary to this, inhibition of IL-6 seems to be efficacious in rheumatoid arthritis and giant cell arteritis, but not psoriasis. Also, TNF-inhibitors have a positive effect on several immune mediated diseases but not multiple sclerosis. This indicates that the immunological activity varies between different immune mediated diseases (McGonagle and McDermott, 2006). By specifying the immune response involved in the pathogenesis of CVD and T2D, clinical trials can help pave the way for development of more focused anti-inflammatory treatment of these diseases through better understanding towards cytokine networks and cytokine hierarchy, which has been proven a key concept in disease classification and treatment decision-making (Schett et al., 2021). The

aim of this study was to identify clinical trials examining the effect of immunosuppressive drugs on CVD and T2D in patients without preexisting immune mediated disorders and translate findings into immunological understanding.

2. Materials and methods

2.1. Search strategy

A systematic literature search was performed using the PubMed database to review the medical literature on the use of DMARDs in CVD and T2D, respectively. The search terms included <drug terms> AND < disease terms>. See appendix S1-2 for a full list of drug and disease terms. The search included records from database inception to August 26, 2021, which was the date of the last search. Only English literature was included. Records were filtered for clinical trial, controlled clinical trial, randomized controlled trial and observational study.

A search on clinicaltrials.gov for on-going trials on the use of DMARDs in CVD and T2D, respectively, was performed. The search included trials with the status "not yet recruiting", "recruiting", "enrolling by invitation", "active", "not recruiting", "suspended", "terminated" and "completed".

2.2. Study selection

With the purpose of generating bedside-to-bench information on the use of DMARDs in CVD and T2D respectively, records were screened for relevance according to title and abstract. Inclusion criteria were randomized-controlled trials (RCTs) and controlled prospective and retrospective cohort studies including the use of DMARDs for treatment of CVD or T2D. CVD studies were required to report either cardiovascular events, vessel wall area or lumen area as outcome. Studies concerning T2D were required to report parameters of glycemic control (e.g., HbA_{1c}), insulin sensitivity or pancreatic β-cell function. At least 4 weeks of follow-up was required. No criteria for number of participants were included. Studies where patients had preexisting immune mediated inflammatory disease (e.g., rheumatoid arthritis) were excluded. Study selection was done by two independent reviewers (Mikkelsen RR and Hundahl MP) with conflicts being resolved by a third reviewer (Torp CK).

2.3. Data extraction/quality assessment

Data collected included number of patients, length of follow-up, DMARDs used, primary end point and, if any, secondary end point.

The Cochrane Risk of Bias Tool 2.0 from 2019 was used to assess internal validity in the included studies across five domains, including randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported results (McGuinness and Higgins, 2021). Each study is presented as low risk of bias, some concerns or high risk of bias. If a study had some concerns in at least one of the five domains but no high risk of bias, it was rated as having some concerns. If it had at least one domain with high risk of bias, the study was rated as having high risk of bias. Protocols, when available, were searched for information. No authors were contacted regarding missing protocols. Data extraction and quality assessment were done by three independent reviewers (Mikkelsen RR, Hundahl MP and Torp CK).

3. Results

3.1. Studies included

The search in PubMed identified 712 articles (see appendix S3 for the full selection process). A total of 19 clinical trials testing canakinumab (n = 8), anakinra (n = 2), methotrexate (n = 1), colchicine (n = 2), hydroxychloroquine (n = 4), etanercept (n = 1) and sulfasalazine (n = 1) were found. As no other relevant trials were found, only these DMARDs are included in this review.

3.2. Quality assessment of included studies

Nine studies were assessed as having a low risk of bias (Ridker et al., 2017, 2019; Choudhury et al., 2016; Everett et al., 2018; Larsen et al., 2007, 2009; Tardif et al., 2019; Nidorf et al., 2020; Pareek et al., 2014), nine were assessed as having some concerns (Russell et al., 2019; NOE et al., 2014; Ridker et al., 2012; Hensen et al., 2013; Rissanen et al., 2012; Gerstein et al., 2002; Quatraro et al., 1990; Dominguez et al., 2005; Tabit et al., 2012), and one was assessed as having high risk of bias (Hsia et al., 2020). Detailed assessment of risk of bias can be found in appendix S4.

3.3. Clinical efficacy

Results from the clinical trials included are summarized in Table 2. Detailed assessment of the studies regarding the use of DMARDs in CVD is presented in appendix S5, including intervention, number of patients, length of follow-up and outcome. Due to the heterogeneity of outcomes which prevented pooled analyses of the studies on the use of DMARDs in T2D, these results are summarized in a narrative way.

Seventeen on-going trials evaluating the use of DMARDs in CVD were identified on clinicaltrials.gov including canakinumab (n = 2), methotrexate (n = 2), colchicine (n = 9), HCQ (n = 3), and abatacept (n = 1). In T2D, two on-going trials were found, including anakinra (n = 1) and HCQ (n = 1). Detailed overview on current on-going clinical trials can be found in appendix S6, including intervention, number of participants, phase, NCT-number and current trial status.

3.4. IL-1β inhibition (canakinumab and anakinra)

Ridker et al. (2017) conducted the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), a randomized, double-blind, placebo-controlled trial. To determine whether the IL-1β-inhibitor canakinumab reduces the risk of cardiovascular events, they included 10,061 patients with a history of myocardial infarction and a hs-CRP-level of at least 2 mg/L. The participants were randomized to receive either canakinumab (50 mg, 150 mg, or 300 mg) or placebo. The primary end point of the study was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. After a median follow-up of 3.7 years, the risk of the primary end point compared to those receiving placebo was 8.7% lower in the group receiving 50 mg canakinumab, 14.2% lower in the 150-mg group, and 13.3% lower in the 300 mg-group. Only the 150-mg

Table 2
Overview of DMARDs investigated in clinical trials regarding CVD and T2D.

DMARD	T2D	CVD
IL-1-inhibitor (canakinumab or anakinra)		
Methotrexate		
Colchicine		
Hydroxychloroquine		
TNF-inhibitor (etanercept)		
Sulfasalazine		

Positive effect	No effect	No clinical trials

group met the prespecified threshold for significance (HR versus placebo of 0.85 and a 95% CI of 0.74–0.98 (p = 0.02)). A key secondary end point was made, including hospitalization for unstable angina that led to urgent coronary revascularization in addition to the primary end point. The risk of the secondary cardiovascular end point compared to the placebo group was 11.1% lower in the 50-mg canakinumab group, 16.4% lower in the 150-mg group, and 17.2% lower in the 300-mg group. Meeting the prespecified threshold for significance, the 150-mg group had a HR versus placebo of 0.83, 95% CI was 0.73–0.95 (p = 0.005). In addition, compared with the placebo group, canakinumab decreased the level of the inflammatory biomarkers hs-CRP and IL-6, whereas no significant reduction was observed in the level of LDL, HDL, and triglycerides (Ridker et al., 2017).

Two studies have investigated the association between canakinumab and atherosclerotic plaque progression. Russell et al. (2019) conducted a randomized, double-blind, placebo-controlled trial including 38 patients with peripheral artery disease. The patients were randomized to receive either 150 mg canakinumab or placebo monthly. During a 12-month follow-up period, no measurable change in mean vessel wall area or mean lumen area in the superficial femoral artery was seen. The mean vessel wall area ratio to baseline was 1.05 (SD: ± 0.08) adjusted to canakinumab and 1.00 (SD: ± 0.16) adjusted to placebo. The mean lumen area, the ratio to baseline was 0.99 (SD: ± 0.07) adjusted to canakinumab and 1.00 (SD: ± 0.08) adjusted to placebo. Compared with placebo, canakinumab significantly reduced the levels of hs-CRP and IL-6 (Russell et al., 2019).

Similar results were seen in a randomized, double-blind, placebo-controlled study conducted by Choudhury et al. (2016). The study included 189 patients with atherosclerotic disease and either type 2 diabetes or impaired glucose intolerance who were randomized to receive either 150 mg canakinumab or placebo monthly. The patients were followed for 12 months, after which the mean change in carotid wall area was 0.59 mm^2 in the canakinumab-group (95% CI: 2.40 to 3.59) and 3.96 mm^2 in the placebo-group (95% CI: 0.94 to 6.98). Thus, the change in carotid wall area was −3.37 mm^2 for canakinumab vs. placebo (p = 0.06), i.e., not statistically significant. Furthermore, no significant difference in wall area between the canakinumab-group and placebo-group were seen in any aortic site during follow-up. A significant decrease in hs-CRP and IL-6 was seen in the canakinumab-group versus the placebo-group (Choudhury et al., 2016).

Several trials were found studying the effects of canakinumab on T2D. Using data from CANTOS (Ridker et al. (2017)), Everett et al. (2018) investigated the association between canakinumab and T2D. In total, 4057 patients from CANTOS had baseline diabetes, and their concentrations of HbA_{1c} and fasting plasma glucose (FPG) were assessed several times during the 48 months of follow up. In the 50 mg canakinumab-group, median HbA_{1c} increased 0.1 percentage point from 7.0% to 7.1% (p = 0.95), in the 150 mg-group it stayed at 7.1%, and in the 300 mg-group it reduced 0.1 percentage point from 7.2% to 7.1% (p = 0.30). In the placebo-group it increased 0.2 percentage point from 7.1% to 7.3%. Thus, canakinumab had no significant effect on HbA_{1c}, and neither did it significantly affect FPG (Everett et al., 2018).

NOE et al. (2014) conducted a randomized, double-blind, placebo--controlled trial including 231 patients with T2D. The patients were randomized to receive either different doses of canakinumab or placebo, and the effect of canakinumab was evaluated in 4 cohorts. After 24 weeks of follow-up, HbA_{1c} had reduced 0.26% in the 10 mg/kg canakinumab-group of cohort 2 and 0.01% in the placebo-group of cohort 2. In cohort 3 and 4, HbA_{1c} increased 0.32% in the 0.03 mg/kg canakinumab-group and 0.27% in the 0.1 mg/kg canakinumab-group, and it reduced 0.18% in the 0.3 mg/kg canakinumab-group, 0.39% in the 1.5 mg/kg canakinumab-group and 0.12% in the placebo-group of cohort 3 and 4. Thus, after 24 weeks a general, modest reduction in HbA_{1c} was seen in the groups receiving at least 0.3 mg/kg canakinumab and in the placebo-groups, but the effect of canakinumab was statistically nonsignificant. Furthermore, a significant reduction in hs-CRP was seen at week 4 in all groups receiving canakinumab, and the effect was maintained for up to 12 weeks in the 1.5 mg/kg and 10 mg/kg canakinumab group (NOE et al., 2014).

Ridker et al. (2012) conducted a randomized, double-blind, placebo-controlled trial allocating 556 patients with T2D to receive either 5, 15, 50, or 150 mg canakinumab or placebo once a month. They were followed for 4 months, after which the median HbA_{1c} decreased in all of the groups. HbA_{1c} decreased 0.3 percentage point in the 5 mg canakinumab group (7.40%–7.1%, p = 0.9), 0.3 percentage point in the 15 mg-group (7.3%–7.0%, p = 0.2), 0.45 percentage point in the 50 mg-group (7.45%–7.0%, p = 0.1), 0.3 percentage point in the 150 mg-group (7.40%–7.1%, p = 0.5), and 0.2 percentage point in the placebo-group (7.4%–7.2%). Thus, canakinumab had a modest but nonsignificant suppressing effect on HbA_{1c}.

Furthermore, canakinumab did not have a statistically significant effect on FPG, fasting plasma insulin (FPI) and insulin resistance. Canakinumab significantly reduced the levels of hs-CRP and IL-6 (Ridker et al., 2012).

Hensen et al. (2013) described the glucose-related secondary and exploratory parameters from the study of Ridker et al. (2012) in detail. In addition to FPG, FPI and insulin resistance, no significant mean change from baseline was seen in relation to postprandial plasma glucose (PPG), postprandial or peak plasma insulin, beta cell function based on insulin secretion rate, or postprandial C-peptide and peak C-peptide (Hensen et al., 2013).

Rissanen et al. (2012) conducted a randomized, double-blind, placebo-controlled study including 190 patients with T2D. The patients were randomized 2:1 to receive either a single subcutaneous injection of 150 mg canakinumab or placebo in addition to their background therapy and they were followed for 4 weeks. During follow up, no statistically significant change was seen in either insulin secretion rate, fasting plasma glucose, postprandial plasma insulin or postprandial C-peptide, however, a significant reduction in hs-CRP and IL-6 was seen in the canakinumab-group (Rissanen et al., 2012).

Larsen et al. (2007) conducted a double-blind, placebo-controlled parallel-group study to test the hypothesis that antagonism of IL-1 signaling would improve glycemic control and β-cell function in patients with T2D. Seventy patients with T2D were assigned to receive either 100 mg anakinra or placebo. The primary end point of the study was a change in HbA_{1c} between baseline and follow up 13 weeks later. In the group receiving anakinra, a mean reduction of HbA_{1c} of 0.33 percentage point from 8.69% to 8.37% was observed after 13 weeks. Contrary to this, an average increase of 0.13 percentage point from 8.23% to 8.37% was seen in the placebo group. Thus, the difference in the change of HbA_{1c} between the two groups was 0.46 percentage point, and the results were statistically significant with a 95% CI of 0.01–0.9 (p = 0.03). Several secondary end points were made. Among these a significant reduction in proinsulin to insulin ratio in the anakinra-group compared with the placebo-group was observed; thus anakinra improved β-cell function, whereas no change in insulin sensitivity was seen. Furthermore, the levels of hs-CRP and IL-6 reduced significantly compared with the placebo group (Larsen et al., 2007). Larsen et al. (2009) conducted a follow-up study following the same patients for 39 weeks after withdrawal of anakinra to investigate the durability of the effects. Regarding HbA_{1c}, the baseline adjusted between-group difference after 39 weeks was −0.05% (95% CI: 0.62 to 0.52, p = 0.867). Thus, the change in HbA_{1c} did not persist. The reduced proinsulin to insulin ratio did maintain, however, and so did the reduced levels of hs-CRP and IL-6 (Larsen et al., 2009).

3.5. Methotrexate

Ridker et al. (2019) conducted the Cardiovascular Inflammation Reduction Trial (CIRT) which, like CANTOS, was a randomized, double-blind trial, though this time aimed to investigate whether treatment with methotrexate (MTX) reduces the risk of CVD. The study

included 4786 patients with a history of myocardial infarction or multivessel coronary disease, randomized to receive either 15–20 mg MTX or placebo. The original end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. After a median follow-up of 2.3 years, this end point had occurred in 170 patients receiving low-dose MTX and 167 receiving placebo, giving a HR of 1.01 and a 95% CI of 0.82–1.25 (p = 0.91). The trial made an expanded primary end point including hospitalization for unstable angina that led to urgent coronary revascularization. This end point occurred in 201 patients receiving low-dose MTX and in 207 patients receiving placebo. This gives a HR of 0.96 and a 95% CI of 0.79–1.16 (p = 0.67). As there was no significant effect in any of the outcomes analyzed, it is not possible to conclude that low-dose MTX lowers the risk of cardiovascular events in high-risk patients. Contrary to canakinumab, MTX did not reduce the levels of hs-CRP, IL-6 or IL-1β (Ridker et al., 2019).

No trials were found studying the effects of methotrexate on T2D.

3.6. Colchicine

Tardif et al. (2019) conducted the Colchicine Cardiovascular Outcomes Trial (COLCOT), which was a randomized, double-blind, placebo-controlled trial aimed to investigate the effect of colchicine on cardiovascular events. The trial included 4745 patients who had had a myocardial infarction within 30 days before they were enrolled. The patients were randomized to receive either 0.5 mg colchicine or placebo once daily. The median duration of follow-up was 22.6 months. The primary efficacy end point was death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in a time-to-event analysis. In the colchicine group 5.5% of the patients experienced the primary end point compared to 7.1% in the placebo group. This result has a HR of 0.77 with a 95% CI of 0.61–0.96 (p = 0.02). Thus, colchicine significantly reduced the risk of new cardiovascular events. The primary end point was especially seen on account of strokes (HR of 0.26 and 95% CI of 0.10–0.70) and urgent hospitalization for angina leading to coronary revascularization (HR of 0.50 and 95% CI of 0.31–0.81) (Tardif et al., 2019).

Nidorf et al. (2020) conducted a randomized, controlled, double-blind trial of low-dose colchicine (LoDoCo2). To assess the effect of low-dose colchicine on cardiovascular events in patients with chronic coronary disease, they included 5522 patients. The patients were randomized to receive either 0.5 mg of colchicine once daily or placebo, and they were followed for a median of 28.6 months. The primary end point was cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. This occurred in 187 patients receiving colchicine and in 263 patients receiving placebo, giving a HR of 0.69 with a 95% CI of 0.57–0.83 (p=<0.001). Resulting in a 31% lower relative risk of the primary end point than placebo, colchicine significantly reduced the risk of cardiovascular events among patients with chronic coronary disease (Nidorf et al., 2020).

No clinical trial has tested the association between colchicine and T2D.

3.7. Hydroxychloroquine

It was not possible to find trials investigating the association between hydroxychloroquine (HCQ) on CVD.

Gerstein et al. (2002) conducted a randomized, placebo-controlled, double-blind trial aiming to investigate the effect of HCQ on T2D. The trial included 135 patients with type 2 diabetes and a HbA_{1c} higher than 11%, randomized to receive HCQ (up to 300 mg bid) or placebo. The primary end point was a blinded decision to stop the treatment on account of an unacceptable glycemic control, meaning the study drug was considered to be ineffective (i.e if HbA_{1c} increased or did not improve). This outcome happened to 69.9% of the patients receiving HCQ and 95.5% receiving placebo, i.e., a significant lower risk of withdrawal for patients receiving HCQ than placebo (p = 0.0001). Regarding the level of HbA_{1c}, a significant reduction was seen in the group receiving HCQ compared to those receiving placebo. Six months after baseline, HbA_{1c} was reduced 1.02% more in the HCQ-group than in the placebo group with a 95% CI of 0.24–1.81 (p = 0.0041). However, stratifying by baseline HbA_{1c} showed that treatment with HCQ was ineffective in patients with HbA_{1c} higher than 13.5% (Gerstein et al., 2002).

Similar results had previously been observed in a trial by Quatraro et al. (1990). This randomized, double-blind, placebo-controlled trial included 38 patients with T2D who were already in treatment with either insulin or glibenclamide and randomized to additionally receive 200 mg HCQ three times daily or placebo. After 6 months, significant reductions in glucose profile and HbA_{1c} were seen in the two groups receiving HCQ, but not in the two placebo groups. In the insulin + HCQ group, an average decrease in glycemic profile of 11.7 mmol/L was observed (95% CI of −13.9 to −9.5), and in the glibenclamide + HCQ group it decreased by 10.8 mmol/L (95% CI of −12.7 to −8.9). HbA_{1c} decreased 3.3% in both groups (95% CI of −3.6% to −3% in the insulin + HCQ group; 95% CI of −3.9% to −2.7% in the glibenclamide + HCQ-group) (Quatraro et al., 1990).

Two studies have been found comparing the efficacy of HCQ with pioglitazone (PIO) in T2D. Pareek et al. (2014) conducted a double-blind, randomized study including 267 patients with uncontrolled T2D (i.e., $HbA_{1c} \geq 7.5\%$ and $\leq 11.5\%$) who were on a combination of metformin plus gliclazide or glimepiride. The patients were randomized to additionally receive either 400 mg HCQ or 15 mg PIO daily. After 24 weeks, HbA_{1c} reduced significantly from baseline in both groups, but the reductions between treatment groups were not significant. HbA_{1c} was reduced by 0.87 percentage point in the HCQ-group from 9.03% to 8.18% (p=<0.0001) and in the PIO-group by 0.91 percentage point from 9.10% to 8.19% (p=<0.0001), with a p-value for between-group difference of 0.909. Furthermore, FPG and PPG reduced significantly from baseline in both groups, but no significant reductions were seen between groups (Pareek et al., 2014).

Similar to Pareek et al. (2014), Hsia et al. (2020) conducted a randomized, controlled trial comparing HCQ and PIO in patients with T2D failing metformin in combination with a sulfonylurea. Twenty-two patients were randomized to receive either 400 mg HCQ or 45 mg PIO once daily as an add-on treatment, and they were followed for 4 months. In the HCQ-group, HbA_{1c} was reduced by 1.2 percentage points from 8.6% to 7.4% (p=<0.0001), and it decreased 2.8 percentage points from 9.1% to 6.3% in the PIO-group (p=<0.0001). Thus, HbA_{1c} was reduced significantly from baseline, although significantly more in the PIO-group as compared to the HCQ-group. A significant reduction in FPG from baseline was seen in the HCQ- and PIO-group too, but the between-group difference was nonsignificant. HCQ showed no effect on insulin sensitivity based on quantitative insulin sensitivity check index (QUICKI) (Hsia et al., 2020).

3.8. TNFα-inhibitor

No clinical trials studying the effect of TNFα-inhibition on CVD were found.

Dominguez et al. (2005) conducted a parallel-group randomized trial to test if treating patients with T2D with the TNFα-inhibitor etanercept would reverse vascular and metabolic insulin resistance. The trial included 20 patients with T2D and obesity (BMI >30 kg/m^2). randomized to receive etanercept (25 mg subcutaneously twice weekly) or placebo for 4 weeks. Forearm glucose uptake did not improve in the etanercept group compared with the control group, neither did β-cell function, endothelial function or vascular and metabolic insulin sensitivity. A statistically significant decrease in the inflammatory biomarkers IL-6 and hs-CRP was seen in the group receiving etanercept compared to the control group (Dominguez et al., 2005).

3.9. Sulfasalazine

Tabit et al. (2012) conducted a randomized, double-blind, placebo-controlled study to test whether sulfasalazine would improve vascular function in patients with coronary artery disease. The study included 53 patients who were randomized to receive either sulfasalazine (500 mg twice daily for 1 week, then 2 × 500 mg twice daily for 5 weeks) or placebo for 6 weeks. Sulfasalazine showed no effect on vascular function, including arterial diameter which increased 0.05 mm in the sulfasalazine-group and 0.06 mm in the placebo-group ($p = 0.99$). No effect of sulfasalazine was seen on the levels of CRP and IL-6 (Tabit et al., 2012).

4. Discussion

4.1. Bedside-to-bench in CVD and T2D

4.1.1. Reverse translation

This is the first study systematically performing a bedside-to-bench approach to evaluate the effect of DMARDs in CVD and T2D. We undertook a review of 19 studies employing targeted immunotherapy for CVD and T2D with the aim of validating known immunopathological and immunogenetic features of these diseases. Currently, only three different classes of immunosuppressive drugs have shown efficacy in either CVD or T2D. These are 1) the IL-1β inhibitors canakinumab and anakinra, 2) colchicine and 3) hydroxychloroquine. MTX, TNFα inhibition and sulfasalazine did not show efficacy in either CVD or T2D. The results from these trials inform our understanding of the immunological mechanisms underlying CVD and T2D. The association between immunological mechanisms and drug targets is depicted in Fig. 2. Overall, the efficacy of IL-1β inhibition with canakinumab, anakinra, and colchicine points to a central role of the innate immune system with contributions from neutrophile granulocytes and macrophages. In contrast, drugs with targets in the adaptive immune system such as T cells and B cells did not show effect.

4.1.2. CVD

Although two studies showed no statistically significant effects of canakinumab on measures of vascular structure, it is of particular interest that CVD is prevented with both canakinumab, anakinra and colchicine, independently of changes in lipid profiles. Canakinumab and anakinra target IL-1β binding to the IL-1 receptor. The main mode of action of colchicine is prevention of inflammasome activation leading to decreased secretion of IL-1β. In this context, it is also interesting that MTX did not prevent CVD and sulfasalazine did not show any effect on vascular structure, including arterial diameter. This suggest that not all immunosuppression is beneficial in CVD, but a delicate immunomodulation is key to exert beneficial (preventive) effects. Then, specific inflammatory mechanisms need to be dampened and especially the IL-1-pathway seem to be of major importance and involved in the pathogenesis of CVD. However, not many targeted immunosuppressive drugs have been tested. Therefore, it is not known whether other cytokine inhibitors or cell targeted therapies might dampen the disease specific inflammation in CVD. Also, other mechanisms for the efficacy seen with colchicine could be involved. Colchicine has been shown to reduce the release of MMP by macrophages, thus preventing matrix degradation and instability of the atherosclerotic plaque. Additionally, colchicine causes macrophages to release anti-inflammatory cytokines such as IL-10 and TGF-β and might reduce the risk of deformity, fibrosis and calcification of the vessel wall, as these cytokines inhibit the growth of vascular smooth muscle cells, fibroblasts and osteophytes (Nidorf and Thompson, 2019).

No effect was observed for MTX, despite its widespread use to treat immune mediated inflammatory diseases. In this respect, it is of note that MTX is associated with a reduced risk of CVD in rheumatoid arthritis patients (Micha et al., 2011). This suggests that the inflammation related to CVD in patients with no preexisting immune mediated inflammatory diseases is not the same as the inflammation related to CVD in rheumatoid arthritis patients.

It is also of particular interest that some anti-inflammatory drugs seem to increase the risk of CVD. This is the case for nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. By inhibiting the cyclooxygenase enzymes COX1 and COX2 and thereby the production of prostaglandins, NSAIDs have been shown to increase the risk of thrombotic events, including myocardial infarction and stroke (Schjerning et al., 2020). Glucocorticoids induce cardiovascular risk

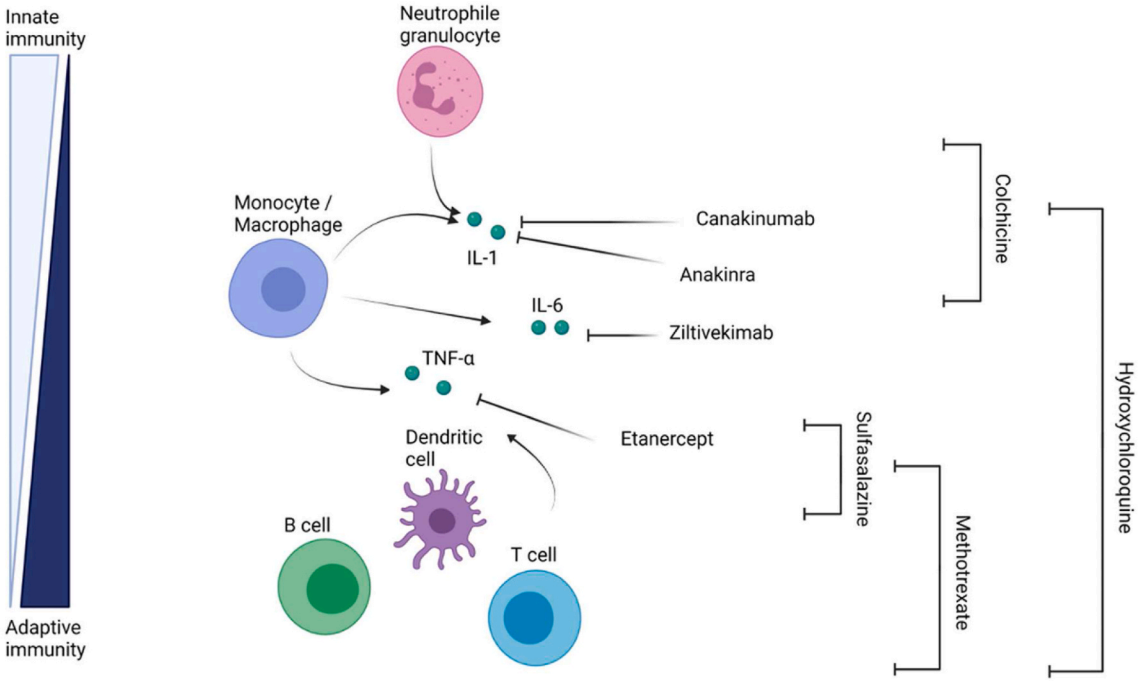

Fig. 2. Immunological understanding of the DMARDs. Modified from McGonagle et al. (2018). Created with BioRender.com.

factors such as obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension. Furthermore, glucocorticoids seem to increase the risk of cardiovascular disease through a combination of systemic vascular actions and a direct effect on blood vessels and the heart, mediated by the activation of glucocorticoid and mineralocorticoid receptors. This might promote atherogenesis and influence the outcome of occlusive vascular events and intravascular injury (Walker, 2007). A recent post-marketing required safety study also found an increased risk of MACE in patients with rheumatoid arthritis treated with the JAK inhibitor tofacitinib compared with patients treated with a TNFα-inhibitor (Mease et al., 2020).

Studies not evaluating clinical endpoints were not included in the SLR. However, several studies have evaluated biomarker endpoints. In the recent RESCUE-study (Ridker et al., 2021), inhibition of IL-6 with ziltivekimab in patients with chronic kidney disease, ziltivekimab significantly reduced markers of inflammation and thrombosis relevant to atherosclerosis, including hs-CRP, IL-6 and lipoprotein(a). Several studies not included in this SLR have also shown that colchicine reduces the level of hs-CRP (Demidowich et al., 2019; Kajikawa et al., 2019). Furthermore, a non-randomized observational study showed that low-dose colchicine therapy reduced coronary plaque volume in patients with recent acute coronary syndrome; an effect that was likely driven by a reduction in hs-CRP (Vaidya et al., 2018). Colchicine has also been shown to significantly reduce the levels of IL-1β, IL-18, and IL-6 in patients with acute coronary syndrome (Martínez et al., 2015), indicating that the reduction in hs-CRP might reflect an inhibitory effect of colchicine on these cytokines, especially by preventing the secretion of active IL-1β. Taken together, these lines of evidence are reassuring on the specific effect of colchicine on IL-1β-mediated inflammatory response.

4.1.3. T2D

Like CVD, inhibition of IL-1β has also showed to have positive effects on T2D in the study by Larsen et al. (2007). The use of anakinra improved glycemic control. This could be mediated by an increased β-cell function due to inhibition of the IL-1β secreted by glucose activated macrophages in the pancreatic islets. However, it did not have an impact on insulin sensitivity, indicating that the IL-1-axis does not contribute to the development of insulin resistance. HCQ also showed a positive effect in T2D by improving glycemic control. The effect was nonsignificant compared to PIO, but significant compared to placebo. However, in the study by Gerstein et al. (2002), HCQ did not affect people with a baseline $HbA_{1c} \geq 13.5\%$. According to that study, this could be because patients did not respond to oral treatment due to noticeable β-cell dysfunction. By preventing the binding of ligands to the intracellular TLR-3, -7 and -9, HCQ inhibits the innate immune system (e.g., IL-1β and TNFα). This is in line with the effect seen with anakinra, thus supporting the theory that this part of the immune system is a key factor in T2D. Neither of the two trials studying the effect of TNFα inhibition showed an association between TNFα and T2D. These negative results could be due to type II error, as both trials only went on for one month and included few patients, which limits the reliability of the results. Inhibition of TNFα showed a decrease in hs-CRP and IL-6. An explanation of why T2D was not improved despite this could be that levels of IL-1 did not decrease, and this might be the most important cytokine in the disease pathogenesis. Furthermore, a large case-control study found an increased risk of T2D with higher levels of IL-1 and IL-6, but not TNFα (Spranger et al., 2003). Inhibition of TNFα has shown to have a positive effect on T2D in rheumatoid arthritis patients (Stagakis et al., 2012), but it might not be possible to extrapolate these results to non-rheumatoid arthritis patients.

4.2. Effect size vs economics and adverse effects

Finally, it is obviously crucial to consider adverse effects and cost-effectiveness with any immunosuppressive treatment for long term prevention of CVD or complications to T2D. Comparing all doses of canakinumab with the placebo group showed no significant difference in serious adverse events, but when looking at specific side effects, there was a statistically significant difference in the occurrence of cellulitis, pseudomembranous colitis, and fatal infection or sepsis (Ridker et al., 2017). Furthermore, colchicine significantly increased the risk of pneumonia (Tardif et al., 2019). These are severe complications and suggest that more targeted treatments with less suppression of normal immune functions are likely needed to make immunosuppression an attractive treatment strategy in the long-term prevention of CVD or complications to T2D.

5. Conclusion

There is growing evidence that low-grade inflammation plays a major pathophysiological role in CVD and T2D. This review highlights that targeting specific parts of the immune system, especially the IL-1β pathway, could have a positive effect on these diseases. Further research into this field is needed, but the observed effects of DMARDs in CVD and T2D could open the way for a new, additional treatment modality for these diseases using existing pharmacological agents. Moreover, this study paves the ground for potential biomarker discovery and pathway elucidation in the crosstalk between inflammation and CVD from a mechanistic point of view.

Authors' contributions

RRM and TWK designed the project. All authors were involved in the conception and scope of the review. RRM, MPH, and CKT performed the literature search, extracted data from included studies. RRM made the first draft of the manuscript. JRC, MK, JMB, and TWK reviewed the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Disclosures/conflict of interest

TWK has engaged in educational activities receiving speaking fees from Pfizer, Bristol-Myers Squibb, Eli Lilly, Novartis, and UCB and has received a consultancy fee from Bristol-Myers Squibb and Gilead. TWK is co-founder and clinical developer in iBiotech ApS developing diagnostic and therapeutic solutions for people with autoimmune diseases and cancer.

MK holds stocks in Novo Nordisk, Regeneron, Novartis, Amgen, Genmab, Alcon and has engaged in educational activities and received speaking fees from Biogen. MK is a co-founder of Vesper Biotherapeutics and InsuSense Therapeutics and is VP of Research.

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References

Atzeni, F., Gerratana, E., Francesco Masala, I., Bongiovanni, S., Sarzi-Puttini, P., Rodríguez-Carrio, J., 2021a. Psoriatic arthritis and metabolic syndrome: is there a role for disease modifying anti-rheumatic drugs? Front. Med. 8, 735150.

Atzeni, F., Rodríguez-Carrio, J., Popa, C.D., Nurmohamed, M.T., Szűcs, G., Szekanecz, Z., 2021b. Cardiovascular effects of approved drugs for rheumatoid arthritis. Nat. Rev. Rheumatol. 17, 270–290.

Bisoendial, R.J., Kastelein, J.J., Stroes, E.S., 2007. C-reactive protein and atherogenesis: from fatty streak to clinical event. Atherosclerosis 195, e10–18.

Brüner, M., Dige, A., Loft, A.G., Laurberg, T.B., Agnholt, J.S., Clemmensen, K., McInnes, I., Lories, R., Iversen, L., Hjuler, K.F., Kragstrup, T.W., 2021. Spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis (SPEED-UP) treatment. Autoimmun. Rev. 20, 102731.

Choi, J., Fenando, A., 2021. Sulfasalazine, StatPearls. StatPearls Publishing Copyright © 2021. StatPearls Publishing LLC, Treasure Island (FL).

Choudhury, R.P., Birks, J.S., Mani, V., Biasiolli, L., Robson, M.D., L'Allier, P.L., Gingras, M.A., Alie, N., McLaughlin, M.A., Basson, C.T., Schecter, A.D., Svensson, E. C., Zhang, Y., Yates, D., Tardif, J.C., Fayad, Z.A., 2016. Arterial effects of canakinumab in patients with atherosclerosis and type 2 diabetes or glucose intolerance. J. Am. Coll. Cardiol. 68, 1769–1780.

Cronstein, B.N., Aune, T.M., 2020. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat. Rev. Rheumatol. 16, 145–154.

Demidowich, A.P., Levine, J.A., Onyekaba, G.I., Khan, S.M., Chen, K.Y., Brady, S.M., Broadney, M.M., Yanovski, J.A., 2019. Effects of colchicine in adults with metabolic syndrome: a pilot randomized controlled trial. Diabetes Obes. Metabol. 21, 1642–1651.

Dominguez, H., Storgaard, H., Rask-Madsen, C., Steffen Hermann, T., Ihlemann, N., Baunbjerg Nielsen, D., Spohr, C., Kober, L., Vaag, A., Torp-Pedersen, C., 2005. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J. Vasc. Res. 42, 517–525.

Donath, M.Y., Shoelson, S.E., 2011. Type 2 diabetes as an inflammatory disease. Nat. Rev. Immunol. 11, 98–107.

Everett, B.M., Donath, M.Y., Pradhan, A.D., Thuren, T., Pais, P., Nicolau, J.C., Glynn, R. J., Libby, P., Ridker, P.M., 2018. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. J. Am. Coll. Cardiol. 71, 2392–2401.

Gerstein, H.C., Thorpe, K.E., Taylor, D.W., Haynes, R.B., 2002. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas–a randomized trial. Diabetes Res. Clin. Pract. 55, 209–219.

Golia, E., Limongelli, G., Natale, F., Fimiani, F., Maddaloni, V., Pariggiano, I., Bianchi, R., Crisci, M., D'Acierno, L., Giordano, R., Di Palma, G., Conte, M., Golino, P., Russo, M. G., Calabrò, R., Calabrò, P., 2014. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr. Atherosclerosis Rep. 16, 435.

Hajjar, D.P., Haberland, M.E., 1997. Lipoprotein trafficking in vascular cells. Molecular Trojan horses and cellular saboteurs. J. Biol. Chem. 272, 22975–22978.

Hensen, J., Howard, C.P., Walter, V., Thuren, T., 2013. Impact of interleukin-1β antibody (canakinumab) on glycaemic indicators in patients with type 2 diabetes mellitus: results of secondary endpoints from a randomized, placebo-controlled trial. Diabetes Metab. 39, 524–531.

Herder, C., Illig, T., Rathmann, W., Martin, S., Haastert, B., Müller-Scholze, S., Holle, R., Thorand, B., Koenig, W., Wichmann, H.E., Kolb, H., 2005. Inflammation and type 2 diabetes: results from KORA Augsburg. Gesundheitswesen 1 (67 Suppl. l), S115–S121.

Hsia, S.H., Duran, P., Lee, M.L., Davidson, M.B., 2020. Randomized controlled trial comparing hydroxychloroquine with pioglitazone as third-line agents in type 2 diabetic patients failing metformin plus a sulfonylurea: a pilot study. J. Diabetes 12, 91–94.

Kaiser, A.B., Zhang, N., der Pluijm, W.V., 2018-2028. 2018. Global prevalence of type 2 diabetes over the next ten years. Diabetes 67, 202–LB.

Kajikawa, M., Higashi, Y., Tomiyama, H., Maruhashi, T., Kurisu, S., Kihara, Y., Mutoh, A., Ueda, S.I., 2019. Effect of short-term colchicine treatment on endothelial function in patients with coronary artery disease. Int. J. Cardiol. 281, 35–39.

Larsen, C.M., Faulenbach, M., Vaag, A., Ehses, J.A., Donath, M.Y., Mandrup-Poulsen, T., 2009. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. Diabetes Care 32, 1663–1668.

Larsen, C.M., Faulenbach, M., Vaag, A., Vølund, A., Ehses, J.A., Seifert, B., Mandrup-Poulsen, T., Donath, M.Y., 2007. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N. Engl. J. Med. 356, 1517–1526.

Leung, Y.Y., Yao Hui, L.L., Kraus, V.B., 2015. Colchicine–Update on mechanisms of action and therapeutic uses. Semin. Arthritis Rheum. 45, 341–350.

Malcova, H., Strizova, Z., Milota, T., Striz, I., Sediva, A., Cebecauerova, D., Horvath, R., 2020. IL-1 inhibitors in the treatment of monogenic periodic fever syndromes: from the past to the future perspectives. Front. Immunol. 11, 619257.

Mandrup-Poulsen, T., 2013. A metabolic autoinflammatory disease. Dermatol. Clin. 31, 495–506. Type 2 diabetes mellitus.

Martínez, G.J., Robertson, S., Barraclough, J., Xia, Q., Mallat, Z., Bursill, C., Celermajer, D.S., Patel, S., 2015. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. J. Am. Heart Assoc. 4, e002128.

McGonagle, D., McDermott, M.F., 2006. A proposed classification of the immunological diseases. PLoS Med. 3, e297.

McGonagle, D., Watad, A., Savic, S., 2018. Mechanistic immunological based classification of rheumatoid arthritis. Autoimmun. Rev. 17, 1115–1123.

McGuinness, L.A., Higgins, J.P.T., 2021. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res. Synth. Methods 12, 55–61.

Mease, P., Charles-Schoeman, C., Cohen, S., Fallon, L., Woolcott, J., Yun, H., Kremer, J., Greenberg, J., Malley, W., Onofrei, A., Kanik, K.S., Graham, D., Wang, C., Connell, C., Valdez, H., Hauben, M., Hung, E., Madsen, A., Jones, T.V., Curtis, J.R., 2020. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann. Rheum. Dis. 79, 1400–1413.

Micha, R., Imamura, F., Wyler von Ballmoos, M., Solomon, D.H., Hernán, M.A., Ridker, P.M., Mozaffarian, D., 2011. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am. J. Cardiol. 108, 1362–1370.

Müller-Calleja, N., Manukyan, D., Canisius, A., Strand, D., Lackner, K.J., 2017. Hydroxychloroquine inhibits proinflammatory signalling pathways by targeting endosomal NADPH oxidase. Ann. Rheum. Dis. 76, 891–897.

Nidorf, S.M., Eikelboom, J.W., Thompson, P.L., 2014. Targeting cholesterol crystal-induced inflammation for the secondary prevention of cardiovascular disease. J. Cardiovasc. Pharmacol. Therapeut. 19, 45–52.

Nidorf, S.M., Fiolet, A.T.L., Mosterd, A., Eikelboom, J.W., Schut, A., Opstal, T.S.J., The, S. H.K., Xu, X.F., Ireland, M.A., Lenderink, T., Latchem, D., Hoogslag, P., Jerzewski, A., Nierop, P., Whelan, A., Hendriks, R., Swart, H., Schaap, J., Kuijper, A.F.M., van Hessen, M.W.J., Saklani, P., Tan, I., Thompson, A.G., Morton, A., Judkins, C., Bax, W.A., Dirksen, M., Alings, M., Hankey, G.J., Budgeon, C.A., Tijssen, J.G.P., Cornel, J.H., Thompson, P.L., 2020. Colchicine in patients with chronic coronary disease. N. Engl. J. Med. 383, 1838–1847.

Nidorf, S.M., Thompson, P.L., 2019. Why colchicine should Be considered for secondary prevention of atherosclerosis: an overview. Clin. Therapeut. 41, 41–48.

Noe, A., Howard, C., Thuren, T., Taylor, A., Skerjanec, A., 2014. Pharmacokinetic and pharmacodynamic characteristics of single-dose Canakinumab in patients with type 2 diabetes mellitus. Clin. Therapeut. 36, 1625–1637.

Ouchi, N., Parker, J.L., Lugus, J.J., Walsh, K., 2011. Adipokines in inflammation and metabolic disease. Nat. Rev. Immunol. 11, 85–97.

Pareek, A., Chandurkar, N., Thomas, N., Viswanathan, V., Deshpande, A., Gupta, O.P., Shah, A., Kakrani, A., Bhandari, S., Thulasidharan, N.K., Saboo, B., Devaramani, S., Vijaykumar, N.B., Sharma, S., Agrawal, N., Mahesh, M., Kothari, K., 2014. Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with pioglitazone. Curr. Med. Res. Opin. 30, 1257–1266.

Ponticelli, C., Moroni, G., 2017. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expet Opin. Drug Saf. 16, 411–419.

Quatraro, A., Consoli, G., Magno, M., Caretta, F., Nardozza, A., Ceriello, A., Giugliano, D., 1990. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann. Intern. Med. 112, 678–681.

Ridker, P.M., Devalaraja, M., Baeres, F.M.M., Engelmann, M.D.M., Hovingh, G.K., Ivkovic, M., Lo, L., Kling, D., Pergola, P., Raj, D., Libby, P., Davidson, M., 2021. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 397, 2060–2069.

Ridker, P.M., Everett, B.M., Pradhan, A., MacFadyen, J.G., Solomon, D.H., Zaharris, E., Mam, V., Hasan, A., Rosenberg, Y., Iturriaga, E., Gupta, M., Tsigoulis, M., Verma, S., Clearfield, M., Libby, P., Goldhaber, S.Z., Seagle, R., Ofori, C., Saklayen, M., Butman, S., Singh, N., Le May, M., Bertrand, O., Johnston, J., Paynter, N.P., Glynn, R.J., 2019. Low-dose methotrexate for the prevention of atherosclerotic events. N. Engl. J. Med. 380, 752–762.

Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., Kastelein, J.J.P., Cornel, J.H., Pais, P., Pella, D., Genest, J., Cifkova, R., Lorenzatti, A., Forster, T., Kobalava, Z., Vida-Simiti, L., Flather, M., Shimokawa, H., Ogawa, H., Dellborg, M., Rossi, P.R.F., Troquay, R.P.T., Libby, P., Glynn, R.J., 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. 377, 1119–1131.

Ridker, P.M., Howard, C.P., Walter, V., Everett, B., Libby, P., Hensen, J., Thuren, T., 2012. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 126, 2739–2748.

Rissanen, A., Howard, C.P., Botha, J., Thuren, T., 2012. Effect of anti-IL-1β antibody (canakinumab) on insulin secretion rates in impaired glucose tolerance or type 2 diabetes: results of a randomized, placebo-controlled trial. Diabetes Obes. Metabol. 14, 1088–1096.

Russell, K.S., Yates, D.P., Kramer, C.M., Feller, A., Mahling, P., Colin, L., Clough, T., Wang, T., LaPerna, L., Patel, A., Lawall, H., Shennak, M.M., Fulmer, J., Nikol, S., Smith, W.B., Müller, O.J., Ratchford, E.V., Basson, C.T., 2019. A randomized,

placebo-controlled trial of canakinumab in patients with peripheral artery disease. Vasc. Med. 24, 414–421.
Schett, G., Elewaut, D., McInnes, I.B., Dayer, J.M., Neurath, M.F., 2013. How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. Nat. Med. 19, 822–824.
Schett, G., McInnes, I.B., Neurath, M.F., 2021. Reframing immune-mediated inflammatory diseases through signature cytokine hubs. N. Engl. J. Med. 385, 628–639.
Schjerning, A.M., McGettigan, P., Gislason, G., 2020. Cardiovascular effects and safety of (non-aspirin) NSAIDs. Nat. Rev. Cardiol. 17, 574–584.
Schrezenmeier, E., Dörner, T., 2020. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat. Rev. Rheumatol. 16, 155–166.
Sedger, L.M., McDermott, M.F., 2014. TNF and TNF-receptors: from mediators of cell death and inflammation to therapeutic giants - past, present and future. Cytokine Growth Factor Rev. 25, 453–472.
Smolen, J.S., van der Heijde, D., Machold, K.P., Aletaha, D., Landewé, R., 2014. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann. Rheum. Dis. 73, 3–5.
Spranger, J., Kroke, A., Möhlig, M., Hoffmann, K., Bergmann, M.M., Ristow, M., Boeing, H., Pfeiffer, A.F., 2003. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 52, 812–817.
Stagakis, I., Bertsias, G., Karvounaris, S., Kavousanaki, M., Virla, D., Raptopoulou, A., Kardassis, D., Boumpas, D.T., Sidiropoulos, P.I., 2012. Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. Arthritis Res. Ther. 14, R141.
Tabit, C.E., Holbrook, M., Shenouda, S.M., Dohadwala, M.M., Widlansky, M.E., Frame, A. A., Kim, B.H., Duess, M.A., Kluge, M.A., Levit, A., Keaney Jr., J.F., Vita, J.A., Hamburg, N.M., 2012. Effect of sulfasalazine on inflammation and endothelial function in patients with established coronary artery disease. Vasc. Med. 17, 101–107.
Tardif, J.C., Kouz, S., Waters, D.D., Bertrand, O.F., Diaz, R., Maggioni, A.P., Pinto, F.J., Ibrahim, R., Gamra, H., Kiwan, G.S., Berry, C., López-Sendón, J., Ostadal, P., Koenig, W., Angoulvant, D., Grégoire, J.C., Lavoie, M.A., Dubé, M.P., Rhainds, D., Provencher, M., Blondeau, L., Orfanos, A., L'Allier, P.L., Guertin, M.C., Roubille, F., 2019. Efficacy and safety of low-dose colchicine after myocardial infarction. N. Engl. J. Med. 381, 2497–2505.
Torp, C.K., Brüner, M., Keller, K.K., Brouwer, E., Hauge, E.M., McGonagle, D., Kragstrup, T.W., 2021. Vasculitis therapy refines vasculitis mechanistic classification. Autoimmun. Rev. 20, 102829.
Vaidya, K., Arnott, C., Martínez, G.J., Ng, B., McCormack, S., Sullivan, D.R., Celermajer, D.S., Patel, S., 2018. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a ct coronary angiography study. JACC Cardiovasc Imag. 11, 305–316.
Walker, B.R., 2007. Glucocorticoids and cardiovascular disease. Eur. J. Endocrinol. 157, 545–559.
World Health Organization, 2017. Cardiovascular diseases. https://www.who.int/news-room/fact-sheets/detail/diabetes. (Accessed 13 April 2022).
World Health Organization, 2020. Diabetes. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). (Accessed 13 April 2022).
Zhou, R., Tardivel, A., Thorens, B., Choi, I., Tschopp, J., 2010. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat. Immunol. 11, 136–140.