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Review article

Heart failure and anti tumor necrosis factor-alpha in systemic chronic inflammatory diseases

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ABSTRACT

Tumor necrosis factor alpha (TNF-alpha) antagonists have emerged as an effective therapy for patients with diseases as Crohn's disease, rheumatoid arthritis, and other chronic systemic inflammatory diseases. In the last years, there has been a growing interest in the role that inflammatory cytokines, which sustain the pathogenesis of these diseases, plays in regulating cardiac structure and function, particularly in the progression of chronic heart failure.

In fact there is an increase of anti-TNF alpha levels in advanced heart failure but the treatment with anti-TNF alpha has been shown to worsen the prognosis of heart failure in randomized controlled trials.

Patients with rheumatoid arthritis have an increased risk for cardiovascular disease and anti-TNF alpha therapy seems to be beneficial on the risk of cardiovascular disease. In Crohn's disease the increased risk of cardiovascular disease is controversial and therefore it is impossible to demonstrate an effect in reduction of the risk; however, heart failure in patients treated with anti-TNF alpha, despite in a small proportion, has been observed.

On the basis of this observation, anti-TNF alpha therapy is contraindicated in patients with Crohn's disease and III–IV New York Heart Association heart failure class.

1. Introduction

Tumor necrosis factor alpha (TNF-alpha) antagonists have emerged as an effective therapy for patients with diseases as Crohn's disease (CD), rheumatoid arthritis (RA), and other chronic systemic inflammatory diseases (CSID) [1]. CSID represent a large group of diseases that may involve all organs and also the heart [2].

Several biologic agents that inhibit tumor necrosis factor (TNF) alpha are available for use in the treatment of RA. Etanercept is a recombinant fusion protein that consists of the soluble TNF receptor (p75) linked to the Fc portion of human IgG1 (TNFR:Fc). Infliximab is a chimeric (human/murine) IgG1 monoclonal antibody directed against TNF. Adalimumab is a fully humanized IgG1 monoclonal antibody that inhibits TNF. Golimumab is a human IgG1 kappa monoclonal antibody specific for human TNF-alpha that neutralizes TNF-alpha activity. Certolizumab pegol (CZP) is a human anti-TNF-alpha antibody Fab′ fragment that is chemically linked to polyethylene glycol. It neutralizes membrane-associated and soluble TNF-alpha.

In CD, three anti-TNF- alpha therapies are approved for treatment of in adults in the United States and all are effective in treatment of luminal Crohn's disease: infliximab, adalimumab, and certolizumab pegol (which is not approved in Europe).

In ulcerative colitis, actually only infliximab is approved in Europe and in the United States.

As a consequence, this variety of approaches could explain the difference in the clinical response in the different diseases in which they are used. For example, etanercept has an Fc domain of IgG1 attached to the active receptor, while only infliximab fixes complement and causes citotoxicity-mediated destruction of TNF alpha producing cell. There may be differences in binding affinities that could account for a potential difference in response rates in CD, but such differences have not been clinically relevant in patients with RA. It is also possible that for some as yet unexplained reason, etanercept is not available to the gut mucosa [3].

In the last years, there has been a growing interest in the role that inflammatory cytokines, which sustain the pathogenesis of CSID, play in regulating cardiac structure and function, particularly in the progression of chronic heart failure (CHF) [4].

CHF represents a major public health burden, and its prognosis is comparable to that of different malignant diseases. It has been shown that CHF progress because of activation of neuro-hormones and pro-inflammatory cytokines following an initial cardiac injury or a mutation of the genetic program [5]. Virtually any heart disease can ultimately lead to heart failure, although the initial event leading to the development of this syndrome is in many cases unknown [6]. Anyway, the activation of the immune system has received considerable interest in its role of maintenance and worsening of CHF, and several strategies to counterbalance different aspects of the inflammatory response are considered.

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Aim of this review is to analyze the following items:

1. The role of TNF-alpha in CHF
2. The role of anti-TNF-alpha therapies in CHF
3. The risk of cardiovascular diseases in all the CSID (as CD, RA, etc) requiring anti TNF-alpha therapies
4. The impact of biologic therapies on the cardiovascular diseases associated with CSID

2. Methods

Medline and the Cochrane Library electronic databases were searched until July 1, 2012. The keywords included "congestive heart failure", "heart failure", "CHF", "coronary artery disease", "atherosclerosis", "tumor necrosis factor antagonists", "biologic therapies", "infliximab", "etanercept", "adalimumab", "certolizumab pegol". No language, date or age restrictions were applied. Due to the paucity of published clinical trials evaluating the use of anti-TNF alpha agents in CHF and heart disease, the review articles summarizing the recent clinical trials were also reviewed. The reference lists from the published clinical trials and review articles were examined in order to identify any additional studies.

3. The role of TNF-alpha in CHF

More than two decades ago, Levine and coworkers demonstrated increased serum levels of TNF-alpha in patients with advanced heart failure [7]. Subsequently, there has been interest in the role that TNF alpha plays in regulating cardiac structure and function, particularly in the progression of CHF.

Initially it was not clear whether elevated levels of TNF alpha in CHF play a direct pathologic role or whether they are merely by-products of immune stimulation. Subsequent studies have suggested that TNF-alpha may also have an indirect role on the cardiovascular system [4].

Yokohama and coworkers showed that TNF-alpha exerted a concentration and time-dependent inotropic effect, when applied to the feline ventricle and the isolated feline miocyte, and this effect was fully reversible after the cytokine removal [8].

Furthermore, a continuous TNF-alpha infusion in rats, at levels comparable with those reported in patients with CHR, resulted in a time-dependent depression in left ventricular function, negative inotropic effect and remodeling, that was partially reversed when TNF-alpha infusion was stopped [9]. Similar findings were noted also in dogs [10].

However, these findings were obtained in animals with normal cardiac function and not myocardial injury, prior to TNF-alpha infusion.

TNF-alpha contributes to the progression of CHF through a variety of mechanisms [11]. In the failing heart, TNF-alpha [1] induces ß-adrenergic receptor uncoupling [12,2] increases reacting oxygen species (ROS) formation [13], and [3] increases inducible Nitric Oxide Sinthases (iNOS) synthesis resulting in high output NO formation [13]—all contributing to contractile dysfunction. In addition, TNF-alpha increases the production of other inflammatory cytokines (such as IL-6 and IL-1) which enhance the TNF-alpha-induced myocardial dysfunction [14,15]. Furthermore, TNF-alpha induces the down-regulation of contractile proteins such as alpha-myosin heavy chain and cardiac alpha-actin in cardiomyocytes of failing hearts, associated with a further decrease in contractile function [16].

Apart from its functional effects, sustained expression of TNF-alpha at high concentrations contributes to structural alterations in the failing heart, such as cardiomyocyte hypertrophy, increased cardiomyocyte apoptosis and cardiac fibrosis [17].

In healthy subjects, increased circulating plasma levels of TNF-alpha predict the risk for cardiovascular diseases [18–20] especially in men [21]. An increased circulating TNFa concentration correlates to the impairment in cardiac function [22,23] and is an independent predictor of reduced event-free survival [20], the development of heart failure in asymptomatic patients without prior MI [24,25], and mortality in patients with advanced heart failure [26–28].

A sustained increase in the myocardial TNF-alpha concentration is associated with reduced left ventricular function, increased left ventricular dilatation and severe morphological alterations (hypertrophy, apoptosis and fibrosis). Most of the detrimental effects of TNF-alpha are TNFR1-dependent. In patients with advanced heart failure, the circulating TNFα concentration is an independent predictor of mortality [29].

4. The role of anti-TNF-alpha therapies in CHF

Despite the encouraging results of small pilot trials with etanercept [30,31], the results of large multicenter trials of etanercept named RENAISSANCE (Randomized Etanercept North AmerIcan Strategy to Study AntagoNism of CytokinEs), RECOVER (Research into Etanercept CytOkine antagonism in VEntriculaR dysfunction) and RENEWAL (Randomized EtaNercEpt Worldwide evALuation) in moderate to severe heart failure did not demonstrate any clinical benefits and suggested that etanercept may adversely affect the course of the disease [32–34].

The etanercept studies recruited a total of 2048 patients. RENAISSANCE recruited faster than RECOVER. [32] The end of follow-up was planned for 6 months after the recruitment of the last patient in either trial. This resulted in a longer median follow-up time in RENAISSANCE. Within RENAISSANCE and RECOVER a clinical composite score was used to assess the clinical effects at 24 weeks (primary endpoint: alpha 0.04). Overall, the number of patients who were classified to have "improved", remained "unchanged" or "worsened" was similar for patients on placebo or any dose of etanercept (RENAISSANCE: $p = 0.17$, RECOVER: $p = 0.34$). In RENEWAL (combined analysis of medium and high dose etanercept vs. placebo), the primary endpoint (death or CHF hospitalization, alpha 0.01) was not different between etanercept and placebo (RR 1.10, 95% CI 0.91 to 1.33, $p = 0.33$). In RENEWAL, the secondary endpoint (all-cause mortality) was not different between etanercept and placebo (RR 1.13, 95% CI 0.86 to 1.50, $p = 0.39$). For the endpoint death or CHF hospitalization, it seems clear that etanercept (compared to placebo) caused more problems in RENAISSANCE (i.e. in North group America) than in RECOVER (i.e. in Europe). This is despite the somewhat higher frequency of infections due to etanercept vs. placebo in the RECOVER trial. Other data, such as injection site reactions or the total number of hospitalizations (for any reason) and of deaths, are not yet available. From the Kaplan Meier curves the 1-year mortality in the RENEWAL population (excluding the low dose group in RECOVER), is 15 to 16%, and the survival curves for placebo and etanercept treated patients overlapped throughout the first year [35]. Given the higher doses of etanercept in the RENAISSANCE/RECOVER programme than in the previous studies, it seems important to know the effects on total mortality for the individual dose levels. These were not reported. Of particular interest would be the total mortality in the 375 patients with 25 mg etanercept once weekly (from RECOVER) compared to the 373 patients on placebo in that study. If there were a benefit in the etanercept group, for many this may change the outlook on these studies and the potential of anti-TNF therapy in general in CHF. Infliximab has been shown to improve left ventricular functions and to limit heart failure in transgenic mice associated with overexpression of TNF-a [36]. However, the ATTACH (Anti TNF-alpha Therapy Against Chronic Heart failure) trial of infliximab concluded that TNF-alpha antagonism with infliximab did not improve heart failure, but it adversely affected clinical status of patients with moderate to severe heart failure [37].

In ATTACH, 150 patients in New York Heart Association (NYHA) III/IV classes were recruited (in NYHA IV: 0.10%). In the placebo group ($n = 549$), none of the patients died during 28 weeks of follow-up. This seems surprising given that this was reported to be a patient group with advanced CHF. In fact, if anything, this patient group

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seems to have had less advanced heart failure than that recruited for RENAISSANCE or RECOVER (28-week mortality in the placebo group of RENEWAL: about 6% [38]). The NYHA classification is very subjective and may not adequately reflect disease severity, particularly if this is (besides Left Ventricular Ejection Fraction [LVEF]) the main inclusion criterion for a study. In an analysis that was extended to 38 weeks, 1 death was observed in the placebo group, 2 patients died in the 5 mg/kg group (4%), whereas 6 of the patients treated with 10 mg/kg had died (12%) [39]. In RENEWAL, the week mortality in the placebo group was about 7% [38].

Furthermore, in ATTACH plasma levels of infliximab were measured at regular intervals. It was reported that the therapeutic drug level of infliximab is 1.0 mg/mL (company representatives have stated that the therapeutic drug level can be up to 8 mg/mL), however it was also shown that in this population of elderly CHF patients the achieved plasma levels of infliximab were between 10 and 100 mg/mL for a period of at least 19 weeks both in the 5 and 10 mg/kg treatment groups [36]. If this statement is correct, it appears that ATTACH tested a very high dose (5 mg/kg) of infliximab and an extremely high dose (10 mg/kg) of infliximab vs. placebo. The adverse events were restricted to the group of patients receiving 10 mg/kg infliximab. We cannot know from ATTACH what the clinical potential of a low or medium doses of infliximab could be in CHF patients. However, we do know that 5 mg/kg infliximab improved LVEF as assessed at week 14 ($p = 0.013$ vs. placebo) [38].

The data arising from these studies show that infliximab did not improve but actually worsened CHF, which remained worsened even after discontinuation of anti-TNF therapy, and that etanercept should be used with caution in patients with RA and CHF; furthermore these data alerted about the safety of TNF-alpha inhibitors in patients with chronic CHF. In fact after these trials, every TNF-alpha antagonist was given an absolute contraindication in patients with CHF NYHA class III–IV and a relative contraindication in patients with CHF NYHA class II, as recommended by current guidelines [39].

Intriguingly, several publications signaled the occurrence of dermatological, intestinal and ophthalmological paradoxical adverse events, so called because they appears after the initiation of the anti-TNF alpha drugs, that are normally used to treat them [40].

To date, is not yet clear if heart failure could be considered another paradoxical adverse event or not. Furthermore, the reasons for which anti-TNF alpha agents do not work in CHF are multiple and not yet fully elucidated. First, TNF alpha production could be an epiphenomenon or could have an adaptive role in heart failure rather than being involved in the pathophysiology of the CHF.

Second, TNF blockers could be selectively cytotoxic to failing myocytes. Infliximab may exert its effects, at least in part, by fixing complement on cells that express TNF alpha on the membrane.

Finally, Patient selection may have mitigated the efficacy of the TNF_blockers. Patients in these trials may have been inappropriately selected. Perhaps the small percentage of patients with the highest TNF alpha levels would have been the appropriate patients for these trials [4].

Table 1 shows the designs and the results of the main studies investigating the anti-TNF-alpha therapies in CHF.

5. The risk of cardiovascular diseases in the chronic systemic inflammatory diseases requiring anti TNF-alpha therapies

5.1. Rheumatoid arthritis

RA is characterized by increased morbidity and mortality for cardiovascular disease, which suggests that systemic inflammation plays an important role in raising the risk for atherosclerosis, myocardial infarction, heart failure and cerebrovascular disease [41–45]. Pro-inflammatory cytokines, including TNF-alpha, do not only contribute to the pathogenesis of RA, but also mediate endothelial dysfunction, vascular instability, and atherosclerosis progression [7,23,46].

Wolfe and Michaud [47] scrutinized the data from National Databank for Rheumatic Disease (NDBRD) and found that the prevalence of HF, adjusted for demographic differences, was 3.9% in patients with rheumatoid arthritis in therapy with synthetic disease modifying anti rheumatic drugs (DMARDs), but was 2.8% in patients with rheumatoid arthritis in combination therapy with anti-TNF-alpha agents, with similar incidence (about 0.2%) in both groups.

In 2008, Listing and coworkers [48] used data from the German Biologics Register, the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), to explore the risk factors for developing HF in RA population. Age, another cardiovascular disease, body mass index, DAS 28 and COX-2 inhibitors therapy proved to be significant risk factors for developing de novo HF in patients with rheumatoid arthritis; treatment with TNF-alpha inhibitors compared to treatment with synthetic DMARDs did not reach statistical significance. In the same

Table 1
Features of the main studies investigating the TNF alpha therapies in Chronic Heart Failure.

Authors, year	Design	No. of patients	Follow up	Results obtained
Deswal, 1999	Randomized double-blind, placebo-controlled, multidose pilot study of etanercept in Patients with NYHA III heart failure.	18	14 days	Etanercept was well tolerated and higher doses were associated with significant improvements in quality of life scores,
Bozkurt, 2001	Randomized, double-blind, placebo-controlled, multidose pilot study of etanercept in patients with NYHA III–IV heart failure.	47	3 months	Treatment with etanercept was safe and well tolerated in patients with advanced heart failure and it resulted in a significant dose-dependent improvement in LV structure and function
Coletta, 2002—RENAISSANCE	Large, randomized, phase 2/3 placebo controlled, double-blind trials of etanercept in patients with NYHA III–IV heart failure.	925	12.7 months	Trial resulted a dose-dependent trend toward increased all-cause mortality and hospitalizations in etanercept groups
Coletta, 2002—RECOVER	Large, randomized, phase2/3 placebo-controlled, double-blind trials of etanercept in patients with NYHA III–IV heart failure.	1123	5.7 months	Terminated and halted in 5.7 months due to poor clinical outcome like RENAISSANCE
Anker and Coats [32]—RENEWAL	A combined analysis of medium and high dose of etanercept.	NA	NA	A trend toward increased mortality and chronic heart failure hospitalizations in etanercept-treated group
Chung, 2003—ATTACH	Randomized, double-blind, placebo-controlled, pilot trial of infliximab in patients of NYHA III–IV.	150	28 weeks	TNF-a antagonism with infliximab did not improve and high doses adversely affected the clinical condition of patients with moderate to severe chronic heart failure

Legend:
NYHA—New York Heart Association.
NA—Not Applicable.
RENAISSANCE—Randomized Etanercept North AmerIcan Strategy to Study AntagoNism of CytokinEs.
RECOVER—Research into Etanercept CytOkine Antagonism in VentriculaR dysfunction.
RENEWAL—Randomized EtaNercEpt Worldwide EvALuation.
ATTACH—Anti-TNF-α Therapy Against Chronic Heart Failure.
LV—Left ventricular.

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study, significant risk factors for worsening of a pre-existing HF were male sex and glucocorticoid therapy at a dose level higher than 10 mg/day; again, treatment with TNF-alpha inhibitors did not prove to be a risk factor for worsening of a pre-existent heart failure compared to synthetic DMARDs therapy.

In 2005, Jacobsson and coworkers [49] investigated the risk of cardiovascular disease in RA patients treated with TNF-alpha antagonists compared to DMARDs treated patients, using patients from a Swedish Register. They noticed that the risk of developing cardiovascular disease was lower in RA patients treated with TNF-alpha inhibitors, which was consistent with the hypothesis that inflammation contributes to the development of cardiovascular events. In 2007, Dixon and coworkers [50] used data from the British Society for Rheumatology Biologics Register (BSRBR) and deepened this issue further: they showed that RA patients treated with anti-TNF-alpha did not have a lower incidence of myocardial infarction compared with RA patients treated with traditional DMARDs; however, 6 months therapy with anti-TNF-alpha markedly reduced the risk of myocardial infarction in patients with disease improvement compared to non-responders.

The above mentioned ATTACH and RENEWAL trials highlighted the detrimental effect of TNF-alpha inhibitors in patients with severe HF, but data from National Registers of RA patients showed that TNF-alpha inhibitors did not increase but actually reduced the risk of developing HF. This suggests that the role of TNF-alpha antagonism in HF may be more complex than previously believed, and uncovered a "rheumatological" dilemma [51].

Available data support the conclusion that patients with severe RA, particularly with a high disease activity, have an increased risk for developing HF. The risk is further increased by treatment with COX-2 inhibitors and glucocorticoids. Because TNF-alpha inhibitors are highly effective in suppressing inflammatory activity in rheumatological disorders, it is very plausible that these drugs provide a beneficial contribution regarding the risk of cardiovascular disease, and an effective treatment of both rheumatological and cardiovascular disease is required for proper management of RA patients. Although National Registries provide apparently encouraging data about HF safety of anti-TNF-alpha therapies, they cannot adequately assess the actual risk, as these drugs are administered to patients with no cardiac dysfunction.

Table 2 shows the studies investigating the risk of cardiovascular disease in RA.

5.2. Crohn's disease

With regards to CD, a possible relationship between IBD and cardiac disease was first suggested by a Finnish epidemiological study that noted a significant increase in ischemic heart disease in both men and women with IBD compared with age- and sex-matched controls [52,53]. A subsequent meta-analysis found no association between IBD and cardiovascular disease mortality. However, with advancements in interventional therapies for cardiac disease, cardiovascular mortality may not be an appropriate surrogate for incidence [54]. Studies in IBD attempting to show increased carotid intimal–medial thickness as a measure of atherosclerotic disease burden have shown conflicting results [55,56].

In the study performed by Ha and coworkers, it was showed that IBD patients do, indeed, have an elevated risk for myocardial infarction, but the risk is limited to women in the 40–59 years age group [54].

There appears to be, in fact, a gender disparity with regard to some arterial thromboembolic events in IBD. It was observed higher rates of acute myocardial infarction in older women with IBD, whereas in men over the age of 40 years, there was no increased risk in myocardial infarction and a significantly lower risk of atherosclerosis when compared with controls. Moreover, there was a higher rate of cerebrovascular accidents in younger women, but in men this risk did not reach statistical significance. In general, the cause for a thrombotic tendency in IBD appears to be secondary to a potent prothrombotic stimulus from local and systemic inflammation, and may be related to disease extent and severity [57]. Active intestinal inflammation may activate the coagulation cascade and upregulate prothrombotic mediators such as Factors V, VII, and VIII, prothrombin, Fibrinogen, and thromboplastin [58]. Furthermore, an upregulation of pro-inflammatory cytokines such as tumor necrosis factor and interleukin-6 can lead to increased tissue factor induction, thereby promoting a systemic pro-coagulant state [59]. Numerous studies have shown that thrombosis in IBD is, in most instances, not related to an underlying genetic or acquired thrombophilia such as Factor V Leiden, homocysteine, prothrombin gene mutations, or antithrombin III deficiency [60–64].

Physiological changes in the intestinal vasculature during active and chronic intestinal inflammation may also contribute to the risk of thromboembolic events. Angiographic studies of IBD patients reveal increased intestinal microvascular stenosis, abnormal vasa recta, and diminished blood flow to the intestine. Chronic inflammation within the microvasculature has been shown to result in increased leukocyte adhesion and recruitment, thereby propagating the inflammatory process [65,66]. Collins and co-workers [67] found that both UC and CD patients exhibit increased platelet aggregation in the mesenteric vasculature compared with non-IBD controls. Thus, the intestinal vasculature may be more susceptible to acute arterial events not only because of increased systemic pro-coagulative factors but also because of a localized process that may lead to thrombosis, ischemia, and infarction.

t2.1 **Table 2**
t2.2 Studies investigating the risk of cardiovascular disease in patients with rheumatoid arthritis.

t2.3 Author, year (ref.)	Therapy comparison	N	Disease duration, years	Follow up time	Results
t2.4 Wolfe and Michaud [47]	INF, ETN vs. DMARD	13,171	15	NR	Similar incidence (0.2%) of HF in patients treated with DMARDS and with DMARDS and anti-TNF-alpha therapies
t2.5 Jacobsson et al. [49]	INF, ETN vs. DMARD	983	11	4 years	The risk of developing cardiovascular disease was lower in RA patients treated with TNF-alpha inhibitors
t2.6 Dixon et al. [50]	INF, ETN, ADA vs. DMARD	10,755	12	1.7 years	RA patients treated with anti-TNF-alpha did not have a lower incidence of myocardial infarction compared with RA patients treated with traditional DMARDs
t2.7 Listing et al. [48]	INF, ETN, ADA vs. DMARD	4,248	9	NR	Treatment with TNF-alpha inhibitors did not prove to be a risk factor for worsening of a pre-existent heart failure compared to synthetic DMARDs therapy.

t2.8 Legend:
t2.9 INF: Infliximab.
t2.10 ETN: Etanercept.
t2.11 ADA: Adalimumab.
t2.12 DMARDS: Disease Modifying Anti-Rheumatic Drugs.
t2.13 RA: Rheumatoid Arthritis.
t2.14 HF: Heart Failure.

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In addition, atherosclerosis and IBD share pathogenetic pathways: inflammatory and immune cells are important constituents of atheroma, and atherosclerotic lesions contain factors capable of triggering an inflammatory response [68,69]. C-reactive protein, which is often elevated during flares of IBD, has been associated with an increased 10-year risk of coronary heart disease regardless of the presence of conventional cardiac risk factors [70]. The pro-inflammatory cytokine interleukin-6, which is upregulated in IBD and plays an important role in intestinal inflammation [71], was also found to independently predict the occurrence of vascular events in otherwise healthy post-menopausal women [72]. It is plausible that the systemic inflammatory state associated with IBD may potentiate concurrent traditional cardiac risk factors in peri- and postmenopausal women, an effect that has been observed in other chronic inflammatory conditions such as rheumatoid and psoriatic arthritis.

In short, IBD patients are at greater risk of venous thromboembolic events. Patients with IBD have a markedly higher risk of acute mesenteric ischemia. Atheroma development in the arterial vasculature may further predispose women with IBD to future acute myocardial infarction and other serious arterial events. Venous thromboembolic events in IBD are associated with high morbidity, with mortality rates between 8 and 25% [73]. Given the additional risk for arterial thromboses, IBD practitioners should be aware of the importance of recognizing these events and focusing on prevention strategies, such as smoking cessation and maintaining long-term remission in IBD.

In Table 3 the studies investigating the risk of CV diseases in CD are showed.

6. The impact of biologic therapies on the cardiovascular diseases associated with systemic inflammatory chronic disease

Spontaneous reporting systems such as the FDA Medwatch program and other postmarketing surveillance studies are helpful in suggesting possible safety signals of rare but serious adverse events after introduction of new agents into the market. These approaches, however, often have the limitations of underreporting, duplicate reporting, lack of denominators to determine event rates and diagnostic misclassification. A series of 38 incident cases of heart failure and nine heart failure exacerbations in patients (38 had RA) receiving etanercept or infliximab reported to the FDA MedWatch program was published in 2003 [74]. Interestingly, in this study, half of the patients that experienced new onset heart failure had no identifiable traditional risk factor for heart failure (previous myocardial infarction, coronary artery disease, hypertension or diabetes mellitus), 10 were 50 years or younger and the median interval from the first anti-TNF-alpha dose to diagnosis of incident heart failure was 3.5 months (range of 1 day to 2 years) [74].

Analysis of more than 1600 RA patients treated in controlled clinical trials indicated that new onset CHF occurred in 0.2% of infliximab and 2.1% of placebo-treated RA and Crohn's disease patients [75].

In recent safety analyses of adalimumab use in patients with RA [76], 0.3% had new onset heart failure, 7% had worsening heart failure. This led to an overall rate of heart failure of 0.28 events per 100 patient-years in all RCTs and subsequent open-label extensions compared with a much lower rate of 0.06 events per 100 patient-years in the postmarketing surveillance [76]. In a nationwide comprehensive monitoring system for RA patients in Sweden treated with etanercept, the reported rate of heart failure (reported as serious events) was 0.04 per 100 patient-years [77]. The difference between these rates may be explained by different methods of reporting and variable strategies to calculate the patient-year exposure to anti-TNF-alpha therapy.

Observational studies provide a valuable study design for addressing the epidemiology of adverse events in a 'realworld' context, but they need to be carefully conducted to have adequate internal validity and generalizability. Beyond the major challenge of addressing channeling bias in these studies (confounding by indication), another limitation is the recurring theme of misclassification of heart failure cases. Recent studies attempted to overcome this major limitation of imprecise heart failure diagnosis.

In a study of the National Databank for Rheumatic Diseases, heart failure was reported by a patient and was considered valid if supported by medical records, physician contact or documentation that it was diagnosed by a physician [47]. The validity of heart failure cases was reported to be greater than 90%. Infliximab and etanercept users had significantly less heart failure (3.1%) than non anti-TNF-alpha users (3.8%), even after adjusting for important covariates using propensity scores [45]. In this cohort, the rate of incident heart failure in patients with RA without a history of cardiovascular disease was 0.4% and was not related to anti TNF-alpha therapy, although the number of cases was small. In patients younger than 50 years of age, no incident cases of heart failure were noted in the anti-TNF-a group. A limitation of the study is that patients who were started on anti-TNF-a therapy were less likely to have known heart failure, although adjusting for the history of heart failure did not alter the results [47].

A small case–control study of Veteran's Affairs patients with RA (n = 103) evaluated the rate of new and worsening heart failure after receiving at least one dose of etanercept, infliximab and/or adalimumab [78]. A RA control group from rheumatology clinic (n = 100) who did not receive TNF-alpha antagonists and a non-RA control group from a VA primary care clinic (n = 100) were used for

Table 3
Studies investigating the risk of cardiovascular diseases in Crohn's Disease.

Author, year	Design of the study	No. of patients	Follow up	Results
Talbot, 1986	Retrospective study	7199	11 years	Thromboembolic complications developed in 92 (1.3%) of the patients; 7 out 92 were arterial ones
Novotny, 1992	Case report	3	NA	Three patients with active pancolonic ulcerative colitis developed arterial thromboembolic complications prior to surgical treatment
Brown, 2005	Case report	1	NA	Acute superior mesenteric artery occlusion during active ulcerative colitis
Nuutinen, 1995	Retrospective (abstract)	NA	NA	The prevalence of coronary heart disease in the older age group of patients with UC (>60 years) was significantly higher both in males and females
Nuutinen, 1996	Retrospective (abstract)	NA	NA	The prevalence of coronary heart disease in the older age group of patients with CD (>60 years) was significantly higher both in males and females
Dorn, 2007	Meta-analysis of 11 studies	4532 patients with CD and 9533 patients with UC	NA	IBD is not associated with increased CV mortality

Legend:
CD: Crohn's Disease.
UC: Ulcerative Colitis.
IBD: Inflammatory Bowel Disease.
CV: CardioVascular.

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comparisons. Heart failure was determined using the ICD-9 code for systolic heart failure coupled with medical record review. History of heart failure was present in 13% patients in all the groups. There were no significant differences between the groups with regards to hospital admissions for heart failure or all-cause mortality. Only one out of seven patients in the anti-TNF-alpha group had incident heart failure. The study was limited by the small sample size, a large range in the follow-up durations between the three anti-TNF-alpha agents, and a sensitivity of the ICD-9 codes which may be inadequate for case finding. Confounding by selection of younger patients with fewer comorbidities is also a potential concern.

The risk of hospitalization for heart failure associated with the use of DMARDs in RA was evaluated using administrative claims data within a cohort of 41 885 patients with RA who were dispensed a DMARD between September 1998 and December 2001 [79]. The authors discussed the very high positive predictive value of the single ICD-9 code for heart failure from previous work in Canada, which may not be generalizable. Over approximately 1 year mean follow-up, the incidence of heart failure was 1.0 event per 100 person-years. In this nested case–control study, infliximab and etanercept were shown to be associated with a lower risk for developing heart failure with a RR of 0.5 (95% CI: 0.2–0.9) relative to non-DMARD therapy, after adjustment for a variety of potentially confounding factors including use of nonsteroidal anti-inflammatory drugs and glucocorticoids [79].

The protective effect was consistent with any DMARD groups, particularly methotrexate monotherapy (RR 0.8, 95% CI: 0.6–1.0). This result suggests that the benefit was related to the control of inflammation by any disease modifying agent and was not unique to anti-TNF-a agents alone. Potential confounding due to channeling bias was partially addressed by excluding patients with a history of heart failure. There was no increase risk of cardiovascular events even after discontinuation of DMARDs, stopping of drugs just before the event due to deteriorating health or patients becoming at risk, could potentially confer a false protective effect of the drugs.

Another recently published study [80] evaluated the risk of incident heart failure among younger adults with RA and Crohn's disease (<50 years old) exposed to etanercept or infliximab compared with those who received nonbiologic immunosuppressives. Heart failure was initially identified by diagnosis codes for heart failure on any claims within 9 months of most recent exposure to a study drug. Subjects with heart failure prior to index date were excluded. Medical records were then reviewed for elements of the modified Framingham criteria for heart failure and ejection fraction. Among 2121 patients with RA and 1897 with Crohn's disease followed for a mean duration of 18 months, heart failure was confirmed in nine cases (0.2%). The relative risk of heart failure trended towards an increased risk at 4.3 for patients with RA who were treated with TNF-alpha antagonist and 1.2 for those with Crohn's disease, although neither estimate was statistically significant [80]. Had the risk estimate been significant, the resultant numbers needed to harm would have been 294 and 3333 for RA and Crohn's disease, respectively. The selection of a younger population allowed for evaluation of incidence of new onset heart failure in those with a low prevalence of cardiovascular comorbidities. Despite being a large cohort of patients with reasonable follow-up, the small number of events limited the power of the study and the ability to control for potential confounding by indication.

A recent study evaluated the mortality from Spanish nationwide cohorts with RA treated with TNF-alpha antagonists from Spanish Society of Rheumatology Database on Biologic Products (BIOBADASER) and those not treated with TNF-α antagonist from the Morbidity and Clinical Expression of Rheumatoid Arthritis (EMECAR) registry [81]. Causes of death were obtained from charts, patients' families and death registries. The patients had similar cardiovascular risk profile, but the EMECAR patients were older with lower disease activity and more prevalent smoking history. The age-stratified incidence rates of heart failure were significantly lower in the BIOBADASER cohort [0.4 (95% CI: 0.2–0.9)/100 person-years] compared with EMECAR cohort [1.9 (95% CI: 1.3–2.7)/100 person-years]. The mortality rate ratios (BIOBADASER/EMECAR) due to all-causes and cardiovascular diseases were decreased at 0.3 (95%CI: 0.02–0.5) and 0.6 (95% CI: 0.2–1.4), respectively, although there was significant increase in rate of infection. There was adjustment for the systematic differences expected between the two cohorts using propensity scores [81].

Curiously, a systematic review and meta-analysis including 16 and 11 publications, respectively, [82] showed that in cohort studies, anti-TNF alpha therapy was associated with a reduced risk for all cardiovascular events (pooled adjusted RR 0.46; 95% CI 0.28, 0.77), MI (pooled adjusted RR 0.81; 95% CI 0.68, 0.96), and CVA (pooled adjusted RR 0.69; 95% CI 0.53, 0.89). Meta-analysis of RCTs also produced a point estimate indicating lower risk of cardiovascular events, but this was not statistically significant (pooled RR 0.85; 95% CI 0.28, 2.59).

Anti-TNF alpha therapy is associated with a reduced risk of all cardiovascular events, MI, and CVA in observational cohorts. There was heterogeneity among cohort studies and possible publication bias. The point estimate of the effect from RCTs is underpowered with wide 95% CIs, and cardiovascular events were secondary outcomes, but RCTs also demonstrated a trend toward decreased risk.

In summary, albeit widely variable and imperfect definitions of heart failure, clinical studies have not shown an increased risk of new onset or worsening of clinical heart failure associated with anti-TNF-a therapies in patients with RA. The incidence of CHF in patients with CSID using anti TNF alpha therapy is low and probably not underestimated; the first reports of CHF in these subsets of patients were made in patients not screened for cardiovascular disease when undergoing anti-TNF therapies, thus allowing successively to gain the awareness for the need of a close surveillance, to avoid using this therapy when cardiovascular disease is suspected.

7. Conclusions

In conclusion, data regarding the risk of CHF with the use of anti-TNF-alpha inhibitors at the FDA approved dose are inconclusive.

However, the labels of etanercept, infliximab, and adalimumab contain the following disease-related concern: “Use with caution in patients with HF or decreased left ventricular function; worsening and new-onset HF has been reported.” In addition, infliximab is contraindicated at doses higher than 5 mg/kg in patients with moderate or severe HF (NYHA class III/IV). The golimumab and certolizumab pegol labels include similar wording.

Given the evidence to date, in patients with symptomatic HF, we suggest that treatment strategies other than TNF-alpha inhibitors should be employed. In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected, and use of the medication should be suspended.

For patients with RA and mild (NYHA functional class I or II) CHF whose arthritis is refractory to other DMARDs or biologic agents (i.e. tocilizumab, rituximab, abatacept), targeted TNF-alpha inhibition might be considered. In CD, the alternative treatment may be another biologic drug which is not an anti-TNF alpha (i.e. ustekinumab, natalizumab). In ulcerative colitis, cyclosporine is a valid alternative to anti TNF alpha or, alternatively and if necessary, surgery could be considerate.

If the use of anti-TNF-alpha treatment is entertained, we suggest to consider a cardiology consultation with baseline echocardiography, maintaining a close follow-up. Furthermore, it should be advisable the avoidance of high TNF-alpha inhibitor doses (e.g., more than infliximab 3 mg/kg, adalimumab 40 mg every two weeks, or etanercept 50 mg/week) and the prompt discontinuation of anti-TNF-alpha therapy if HF worsens.

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Learning points

• What is already known?

The role that inflammatory cytokines, which sustain the pathogenesis of CSID, play in regulating cardiac structure and function, particularly in the progression of chronic heart failure

• What should we learn?
- data regarding the risk of CHF with the use of anti-TNF-alpha inhibitors at the FDA approved dose are inconclusive
- in patients with symptomatic HF, we suggest that treatment strategies other than TNF-alpha inhibitors should be employed
- in a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected, and use of the medication should be suspended.
- if the use of anti-TNF-alpha treatment is entertained, we suggest to consider a cardiology consultation with baseline echocardiography, maintaining a close follow-up

Conflict of interests

We disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, our work.

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