Evidence for use of siltuximab or anakinra as second line therapies (after failure of tocilizumab) for Cytokine Release Syndrome (CRS) following use of Chimeric Antigen Receptor T-cell (CAR-T) therapy

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Brief

Chimeric antigen receptor T-cell (CAR-T) therapy often causes cytokine release syndrome (CRS) which is treated with tocilizumab as first-line therapy. Tocilizumab is licensed for this indication and is funded by NHS England. In some cases, it is not sufficiently effective. Anakinra or siltuximab have been considered in this case, but both medicines are unlicensed for this indication. This evidence summary has been written to inform NHS England Specialised Commissioning of the published evidence for the use of siltuximab or anakinra as second-line treatments for CAR-T cell therapy associated CRS after failure of tocilizumab.

Scope and Limitations

This review considers all published clinical evidence in humans which is directly relevant to the brief (use of siltuximab or anakinra in humans for CRS that occurs following using of CAR-T cell therapy). First or second line use has been considered for inclusion as data were limited. Data for the use of siltuximab or anakinra in other similar conditions (e.g. macrophage activation syndrome) were not considered to be directly relevant to the brief so were not included. This is with the exception of Hemophagocytic Lymphohistiocytosis (HLH) which is specifically mentioned in the interim commissioning statements for both Yescarta® (axicabtagene ciloleucel cells) and Kymriah® (tisagenlecleucel cells), therefore was considered.[1,2]

SUMMARY OF EVIDENCE

A systematic search of the published literature found no prospective studies of siltuximab or anakinra used either first or second line for the management of CRS following CAR-T cell therapy. In addition, no studies comparing siltuximab or anakinra with tocilizumab in the management of CRS post CAR-T cell therapy were found.

There is theoretical rationale to suggest that **siltuximab** may offer advantages over tocilizumab for this indication as its mechanism of action is to directly inhibit IL-6 and it has a smaller molecular size, therefore may confer better ability to manage neurotoxicity.[3-6] However, published data for siltuximab are limited to two case reports in refractory CRS after CAR-T cell therapy following tocilizumab and/or corticosteroids. [7,8] These cases both resulted in fatal outcomes and it is possible that siltuximab might have been initiated too late to have an effect. There are anecdotal reports of the first line use of siltuximab as an alternative to tocilizumab in the USA but outcome data for first line use are not published. [9,10]

Interleukin 1 (IL-1) is considered to play a role in triggering CRS. **Anakinra,** which inhibits the activity of IL-1 may theoretically reduce both CRS and neurotoxicity after CAR-T cell therapy.[11-14] Although there are no published data for anakinra for this indication, there are some promising data from a retrospective case series of 44 patients with secondary Haemophagocytic Lymphohistiocytosis (sHLH) for use of anakinra alongside intravenous immunoglobulins (IVIG's) and corticosteroids, with or without antimicrobial therapy.[15-19] These are potentially relevant because CRS following CAR-T cell therapy can evolve into fulminant HLH.[1,2] However, it should be noted that none of the cases in which anakinra was used in sHLH in these case series involved patients with HLH due to CAR-T cell therapy. Also it is not possible to ascertain whether responses seen in these cases were related to the anakinra or the other concomitant drugs. So although these data for anakinra in sHLH due to causes other than CAR-T cell therapy are promising, it is not clear if these data can be extrapolated to this scenario.

A clinical trial of anakinra in CRS post CAR-T cell therapy (used second line to tocilizumab) is in the early stages of planning at a provider centre in England. This centre anecdotally reports one case of successfully using anakinra for CRS post CAR-T cell therapy after failure of tocilizumab but these data are unpublished. Data from this trial will allow a more complete assessment of the efficacy of anakinra for this indication. [20]

FULL EVIDENCE REVIEW

Background and context

The innovative CAR-T cell therapies (Kymriah® and Yescarta®) have revolutionised the treatment landscape for patients with highly refractory advanced lymphoid malignancies. They are regulated as medicines in the EU, specifically as somatic cell therapy Advanced Therapy Medicinal Products (ATMPs). CAR-T cell therapies are currently provided by the NHS in England via 10 designated hospitals for children and young people with B cell acute lymphoblastic leukaemia (ALL) and for adults with diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma. They are generally considered for use by a panel of expert clinicians in the NHS when all other treatment options have been unsuccessful and the condition has relapsed or been refractory to existing treatment options. [1,2,21,22]

CAR-T cell therapy is associated with unique acute toxicities that need specialised monitoring and management. Cytokine-release syndrome (CRS) and CAR-T cell-related encephalopathy syndrome (CRES) are the most common toxicities observed after CAR-Tcell therapy and, rarely, CRS can evolve into fulminant HLH. Some patients are more susceptible to neurological toxicity (CRES) which may occur due to translocation of cytokines and CAR-T cells across the blood-brain barrier. [1,2] CRS, which can be serious and fatal, is a form of Systemic Inflammatory Response Syndrome (SIRS). [1,2] It occurs as a result of massive inflammatory cytokine production and is characterised by elevated IL-6 levels, which correlate closely with CRP levels. [23] The pathophysiology of CRS and CRES also suggest that macrophage-produced IL-1 plays a major role in triggering CRS. CRS may also be associated with bone marrow suppression and Disseminated Intravascular Coagulation (DIC) and it may cause a clinical and pathological picture that is similar to macrophage activating syndrome (MAS).[4,11] Symptoms of CRS include high grade fevers, rigors, myalgias, malaise and arthralgia. Severe cases may involve pulmonary, cardiovascular and renal and hepatic toxicity and may be associated with high grade hypotension. CRS can be graded using the Lee system from 1 to 4 and grade 3 refers to cases requiring more aggressive intervention such as more pressor support (high or multiple doses), oxygen supplementation (> 40%) and typically ITU admission. Grade 4 is limited to life-threatening symptoms, including grade 4 organ toxicities and the requirement of ventilator support.[1,2, 24]

Management of CRS associated with CAR-T cell therapy

Intensive monitoring, accurate grading, and prompt management of toxicities with aggressive supportive care, anti IL-6 therapy, and/or corticosteroids for severe cases are required to reduce the morbidity and mortality associated with CAR-T cell therapy. Anti-IL-6 / IL-6R therapy has been reported to reverse CRES during the first phase, whereas corticosteroids are the preferred treatment for the second phase, possibly due to higher permeability of the blood brain barrier during the first phase enabling better diffusion of the therapeutic monoclonal into the CNS. [1, 2]

Tocilizumab is the only agent licensed for the management of moderate to severe CRS following CAR-T cell therapy. This is based on successful use without impacting the efficacy of treatment in pivotal trials of Yescarta® and Kymriah® in patients aged 2 and over. It works by competitively inhibiting the ability of IL-6 to bind to its receptor. There are concerns about upsurges in IL-6 levels after tocilizumab use and resulting delayed neurotoxicity. [1,2,4,5] It is also considered that owing to its larger molecular size, tocilizumab is unable to penetrate the blood-brain barrier and therefore may be ineffective in blocking the effects of increased levels of IL-6 in the CNS (neurotoxicity).[3-6] In a significant minority of cases, tocilizumab and/or steroids are not sufficiently effective and, in these cases, anakinra or siltuximab have been considered but it is widely recognised that clinical experience with these for CRS post CAR-T is lacking.[3, 26-28]

Siltuximab for CRS following CAR-T cell therapy

Siltuximab is an IL-6 antagonist which exerts its effects directly on IL-6. It is a human-mouse chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human IL-6. It prevents the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus neutralising the activity of IL-6. It is licensed for the treatment of adults with Multicentric Castleman's disease (MCD) who are HIV negative and human herpes virus-8 (HHV-8) negative. For the licensed indication, it is administered as an intravenous infusion (11mg/kg) over an hour, with doses repeated every 3 weeks until treatment failure. The safety and efficacy of siltuximab in children aged under 17 years has not been established in licensing studies since no data are available in this population. [29]

As siltuximab blocks IL-6 directly, it has a theoretical benefit of preventing exposure of the CNS to the high IL-6 levels seen after tocilizumab administration and potentially leading to lower neurotoxicity. [4,5] In theory, IL-6 may compete with tocilizumab for binding to the IL-6 receptor whereas this is less likely with siltuximab because it exerts its effects directly on IL-6. [33] It is also suggested that because siltuximab has a smaller molecule size, it may penetrate the blood-brain barrier, unlike tocilizumab, and so may theoretically be more useful in patients with active neurotoxicity. [3] Some experts suggest management algorithms for CRS where tocilizumab or siltuximab are interchangeable. Others argue, however, that in the absence of clinical trials comparing the two agents, siltuximab should be considered as third line therapy, after tocilizumab and corticosteroids.[4, 6]

Data from clinical trials

No published studies looking specifically at siltuximab either first, second or subsequent line for the management of CRS following using of CAR-T cell therapy were found. In addition, no studies comparing siltuximab with other agents (e.g. tocilizumab) for this indication were found.

Siltuximab use was reported during two pivotal trials of Yescarta®, ZUMA-3 (adults) [10] and ZUMA-4 (paediatrics and adolescents)[9] but as these trials are only published in abstract form, no detail is available with regards to the line of use of siltuximab, the dose(s) used and patient specific outcome data following its use. [9,10] The ZUMA-3 and ZUMA-4 studies enrolled adults and children (over the age of 2) with relapsed and/or refractory Acute Lymphoblastic Leukaemia (R/R ALL). The primary endpoint of the phase 1 portion of the studies was the incidence of dose-limiting toxicities whilst secondary endpoints included efficacy outcomes and biomarker assessments. As of January 2017, 7 patients had been treated with CAR-T cells, all of whom had high disease burden and received bridging chemotherapy with cyclophosphamide and fludarabine. CRS was reported in all patients; 3 adults (grade 1, n=1; grade 2, n=2) and 4 children (grade ≤ 3). Neurotoxicity was reported in all 3 adults (grade 3, n=2; grade 4, n=1) and in 1 child (grade 3). CRS and neurotoxicity were successfully managed to resolution with tocilizumab, corticosteroids, and/or siltuximab in addition to other supportive care for all 7 patients. With respect to efficacy outcomes, Minimal Residual Disease-Negative (MRD) remission was observed in all 7 patients who received CAR-T therapy. An earlier paper from July 2016 that reports data from both ZUMA-3 and ZUMA-4 looks at only 5 of the patients mentioned (3 adults and 2 children) states that MRD- remission was observed in all 5 patients by day 28, with some remissions occurring as early as day 7. Four of 5 patients have had a complete response with partial hematologic recovery to date, and 1 of 5 patients with MRD- remission was showing recovering counts [9]. This detail is not provided in the newer paper with additional paediatric and adolescent patients [10].The manufacturer of Yescarta® were contacted with a request to provide further detail from these studies around the use of siltuximab and outcomes after using it but they were not able to provide any additional data. [30]

To date, no published data from other pivotal trials of Yescarta® nor of Kymriah® indicate use of siltuximab for CRS following CAR-T cell therapy, though there are ongoing studies for these two therapies. [31] Development of other modified T-cell therapies is also underway (e.g. tabelecleucel and lisocabtagene maraleucel) but there is no detail in their published trial protocols about how CRS is to be managed (i.e. whether with tocilizumab, siltuximab or other agents). [31,32]

Case series / reports

In two cases of refractory and severe CRS following CAR-T cell therapy; siltuximab was used second line following tocilizumab or third line after tocilizumab and steroids. [7,8] In these scenarios, siltuximab was not effective at managing the CRS which proved fatal in both cases. This suggests the possibility that siltuximab might have been initiated too late to have an effect and also possibly that optimal dosing was not used.

In a small study carried out at the Fred Hutchinson Cancer Research Center in Seattle (USA), safety and feasibility of CAR-T therapy was studied in a phase I/II open-label trial of 24 adults with Chronic Lymphocytic Leukaemia (CLL). Patients had previously received ibrutinib and had either experienced disease progression and/or could not tolerate or were unresponsive tovenetoclax. They were given lympho-depleting chemotherapy (cyclophosphamide and fludarabine) followed by CAR-T cell therapy. Four weeks after CAR-T cell infusion, with an overall response rate of 71%, it was concluded that CAR-T cell therapy was highly effective in these patients. Of the 24 patients, 83% developed stage 1-5 CRS (stage 1-2 [n=18], stage 4 [n=1], stage 5 [n=1]) and 8 of 24 developed neurotoxicity following CAR-T cell therapy. All patients with neurotoxicity also had CRS. Five patients with stage 2 or higher grade CRS were treated with1-3 doses of i.v. tocilizumab 4-8mg/kg and i.v. dexamethasone 10mg twice daily was used in 6 cases of CRS; again stage 2 or higher. One patient who developed stage 5 CRS and neurotoxicity was treated with 3 doses of tocilizumab as well as 13 doses of dexamethasone and also siltuximab 11mg/kg given i.v. This patient developed fatal neurotoxicity after becoming febrile on day 1, progressing to grade 3 to 4 CRS from

day 4 that was refractory to tocilizumab and dexamethasone. On day 9, the patient developed cerebral oedema that was refractory to siltuximab and mannitol, and died 11 days after CAR-T cell infusion. There was no history of CNS leukaemia, but CSF sampling was not performed and the patient died before the cancer was re-staged. [7]

A paper from the Abramson Cancer Center of the University of Pennsylvania, Philadelphia (USA), reported that as of January 2014, they had treated 97 patients (30 children with Acute Lymphoblastic Leukaemia [ALL], 12 adults with ALL, 41 with CLL and 14 with Non-Hodgkin's Lymphoma [NHL]) with CAR-T cell therapy. Severe CRS (grades 3-5) occurred in 27 (64%) of ALL patients and 16 (29%) of CLL/ NHL patients (p=0.001). Of these, 12 adults with ALL received CAR-T cell therapy and severe CRS occurred in 11 of 12 adult ALL patients. CRS was self-limited in 2 patients, rapidly reversed with anti-IL6 therapy in 6 patients (though it was not specified which IL-6 directed therapy was used) and was refractory to therapy, contributing to death, in 3 patients who were not evaluable for response. No baseline attributes differentiate these 3 patients from the 9 adult ALL patients with manageable grades 1-4 CRS though all 3 patients had significant disease burden at baseline. Of those who died, one patient developed CRS within 24 hours of CAR-T cell infusion. He had received tocilizumab 8mg/kg on days 3 and 4 and then siltuximab on days 5 and 15 as well as intermittent high dose steroids between days 4 and 15. After an initial response, he developed recurrent fever, pulmonary infiltrates and blood cultures positive for stenotrophomonas. He died on day 15 with refractory hypoxia and hypotension.[8]

Published anecdotal data from oncology centres (global)

A CAR-Tcell-therapy-associated TOXicity (CARTOX) Working Group in the USA has developed management and treatment algorithms for CRS. They recommend either i.v. tocilizumab 8 mg/kg or i.v. siltuximab 11 mg/kg for persistent CRS (lasting >3 days) and for management of CAR-T-cell-related encephalopathy syndrome (CRES). They agree that although tocilizumab is currently the first-line anti-IL-6 therapy for treatment of CRS, either tocilizumab or siltuximab have been used successfully first line for the management of moderate-to-severe CRS at their centre (The University of Texas MD Anderson Cancer Center). [25, 33] However, no patient specific data were identified from the published literature on the use of siltuximab first or second line by this group. Other centres in the USA also report using siltuximab in patients with refractory CRS following CAR-T cell therapy as either first [34] or second line [27,35] so its use is presumably successful, but again, no patient specific data have been identified from the published literature on the use of siltuximab from these centres or any others.

Anakinra for CRS following CAR-T cell therapy

Anakinra neutralises the biologic activity of IL-1α and IL-1β by competitively inhibiting their binding to IL-1R. It is licensed for the treatment of adults with RA in combination with methotrexate (but not recommended by NICE for this), for treatment of Cryopyrin-Associated Periodic Syndromes in adults and children (aged >8 months) and for Still's Disease. It is administered by subcutaneous injection (1-2 mg/kg/day) using a graduated pre-filled syringe. [36]

The pathophysiology of CRS and neurotoxicity suggest that macrophage-produced IL-1 plays a major role in triggering CRS and that IL1 blockade with anakinra may reduce both CRS and neurotoxicity, although this approach has yet to be tested in a clinical trial. There are studies in humanised mice which suggest that anakinra may have a role in CAR-T therapy associated CRS but animal studies are generally not considered suitable predictors of response in humans and clinical trials are needed to ascertain the effect of anakinra for both CRS and serious neurotoxicity. [12-14,17]

Data from clinical trials, case series or case reports

No studies, case series or case reports have been identified from the published literature of anakinra being used either first, second or subsequent lines to manage (or prevent) CRS which occurs as a result of CAR-T cell therapy. No published studies comparing anakinra with any other agents (e.g. tocilizumab) used in the management of CRS post CAR-T cell therapy were found. Published data from pivotal trials of Yescarta® and Kymriah® did not indicate that anakinra was used at all, though some studies are still ongoing. [31] Development of other modified T-cell therapies is underway but there is no detail in the published trial protocols for ongoing studies around how CRS is or will be managed and whether anakinra will have a role. [31,32]

Anecdotal data from oncology centres (global)

There is some experience at Kings College Hospital in London of using anakinra at a daily dose 200mg (until 24 hours after resolution of CRS) successfully in a patient with CRS following CAR-T cell therapy which was refractory

to tocilizumab although this is not published. A clinical trial of anakinra, for the management of CRS post CAR-T cell therapy which is refractory to tocilizumab, is in the early stages of planning at this centre. This phase 2, multicentre, randomised controlled trial will compare dexamethasone with anakinra for this indication. The dosing regimen is yet to be determined and it is not clear how many patients will be enrolled or when data will become available from this trial but when available, these data will allow a fuller assessment of the efficacy of anakinra for this indication. [20]

With respect to published anecdotal reports, one paper notes that several agents other than tocilizumab, including anakinra have been used to manage CAR-T cell induced CRS [37] but no patient specific data have been identified from the published literature on the use of anakinra either first or second line.

Anakinra for Haemophagocytic Lymphohistiocytosis (HLH)

The interim commissioning statements for Yescarta® and Kymriah® mention that CRS following CAR-T cell therapy can evolve into fulminant HLH.[1,2] This is a hyperinflammatory condition which often presents with unremitting fever, hepatosplenomegaly, progressive cytopenias and autopsy findings of hemophagocytosis (i.e., phagocytosis of hematopoietic cells by activated macrophages). HLH can be familial or secondary (sHLH), often triggered by infection or malignancy, medication use, or other causes. Clinical outcomes for secondary HLH are poor. Current management of HLH varies according to underlying cause; in haematology a regimen of dexamethasone, methotrexate, etoposide and ciclosporin is used but is limited by the lack of tolerability of etoposide. [38] Anakinra has been considered for treatment of HLH because it is generally well tolerated and because some studies have shown elevated serum IL-1 or IL-1ra levels in patients with HLH. [15,18]

The evidence to support anakinra in HLH is based on a collection of retrospective case series and case reports of patients (17 children and 27 adults in total) with sHLH in whom it was used alongside IVIG and corticosteroids with or without antimicrobial therapy as required. [15-19] In these cases, where a dose was reported, anakinra was generally given subcutaneously between 5 to 11mg/kg/day in children and 4 to 8mg/kg/day in adults. Anakinra was generally found to be a useful therapy alongside steroids and IVIG's in patients with HLH with one case series reporting significantly decreased CRP and fibrinogen levels after a week of treatment with this regimen. Beneficial effects reported in patients managed with this regimen included; improvement in ventilator requirement, earlier discharge from intensive care and improvement in organ dysfunction. Reported survival rates in adults and children with sHLH who were treated with this regimen ranged from 50% to ~80%. The wide range in survival rates might be explained by heterogeneous populations of patients studied, varying severities of HLH and differing criteria for reporting of 'survival'. In all cases though, anakinra was well tolerated, and no significant adverse effects were seen.

Despite this promising evidence, however, none of the case series mentioned use of CAR-T cell therapy as a cause of HLH in any of the patients included; it is not known whether these data can be extrapolated to patients with HLH post CAR-T cell therapy. With respect to limitations, all of these case series are small, uncontrolled and inadequately powered to establish the clinical benefits of anakinra in patients with secondary HLH. In addition, the use of corticosteroid therapy and IVIG's alongside anakinra is a possible confounding issue as these may independently contribute to outcomes of sHLH.

This document is not intended as a dosing guideline.

Information and advice about management of the toxicity of CAR-T therapies (including choice of products and dosing) should be sought from the SPS Pan-UK Pharmacy Working Group for ATMPs. This group are currently developing consensus ATMP toxicities management guidance which will be published on the SPS website.

Table 1: ESTIMATED COMPARATIVE COSTS (This document is not intended as a dosing guideline).

Agent	Route of administration	Estimated cost range per patient per course.	Assumptions and limitations Limitations
Tocilizumab	Intravenous infusion	£1500 to £2269	• Assumes 3 doses of 8mg/kg in an adult weighing 70kg or 12mg/kg in children but >3 doses may be used in refractory cases. • Highest cost based on use of 3 vials of 400mg and 3 vials of 200mg.
Siltuximab	Intravenous infusion	£6960	• Not licensed for this indication. • Dosing of 11mg/kg used 3 times in adults is based on limited clinical data available. • Cost based on use of 6 vials of 400mg.
Anakinra	Subcutaneous injection	£393	• Not licensed for this indication. • Dose of 100mg TDS for 5 days based on limited clinical data (in patients with sHLH) available. • Cost based on use of 15 x 100mg syringes.

All costs based on list price without discounts and cost of administration and accessories of administration not included.

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Search strategy (March-April 2019)

- Summary of Product Characteristics for Yescarta®, Kymriah®, Siltiximab®, Tocilizumab® and Anakinra®
- Manufacturers medical information departments for Yescarta, Kymriah, Siltiximab, Tocilizumab and Anakinra)
- Clinical Guidelines search via www.evidence.nhs.uk including NICE guidelines and Technology Appraisals.
- Specialist Pharmacy Service (SPS) website (www.sps.nhs.uk)

- Medline 1950 to present via HDAS:
  - cytokine release syndrome AND (axicabtagene OR tisagenlecleucel)
  - cytokine release syndrome AND (INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN OR siltuximab)
  - (cytokine release syndrome OR CYTOKINES/) AND (INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN OR siltuximab)
  - cytokine release syndrome AND "IMMUNOTHERAPY, ADOPTIVE"/
  - exp. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME/ AND INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN/ or siltuximab
  - exp. LYMPHOHISTIOCYTOSIS, HEMOPHAGOCYTIC/ AND (INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN"/ or siltuximab)
- Embase 1947 to present via HDAS:
  - CYTOKINE RELEASE SYNDROME/ AND (ANAKINRA/ OR SILTUXIMAB/)
  - CYTOKINE RELEASE SYNDROME/ AND (AXICABTAGENE CILOLEUCEL/ OR TISAGENLECLEUCEL T/)
  - HEMOPHAGOCYTIC SYNDROME/ AND (ANAKINRA/ OR SILTUXIMAB/)
- Cochrane Library: Cytokine release syndrome AND anakinra or siltuximab
- Pivotal licensing studies for Yescarta and Kymriah
- In-house databases: UpToDate.com, Dynamed, Drugdex.com, BMJ best practice Martindale, AHFS
- New Drugs Online Database via www.sps.nhs.uk
- Personal communications with specialist pharmacists at CAR-T cell therapy centres (UCLH,KCH,BRI)

Research recommendations:
Prospective clinical studies are needed to evaluate the safety, efficacy and optimal doses of siltuximab and anakinra for management of CRS following CAR-T cell therapy. Prospective clinical studies are needed to directly compare the effectiveness of these with tocilizumab in the treatment of CRS. It is recognised that there may be some use of anakinra or siltuximab for management of CRS following CAR-T cell therapy at centres which provide CAR-T therapy but none of these case reports are published. Providers of CAR-T cell therapies should be encouraged to publish any case series and case reports of using siltuximab or anakinra used first, second or third line in the prevention and/or management of CRS and/or neurotoxicity following CAR-T cell therapy.

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