Prophylactic Eculizumab for Adult Patients with Atypical Haemolytic Uraemic Syndrome Undergoing Kidney Transplantation

Aims of the Guidelines

The guidelines make recommendations about the management of patients with atypical haemolytic uraemic syndrome (aHUS) who are being considered for transplantation. The guidelines have been developed specifically to consider the use of prophylactic Eculizumab to prevent aHUS recurrence after transplantation.

The guidelines are aimed at healthcare professionals responsible for the assessment and treatment of these patients.

The evidence for these recommendations has been assessed using the modified GRADE system. The modified GRADE system defines both the strength of the recommendations of the guideline authors and the level of evidence upon which each of the recommendations is based. This grading system classifies expert recommendations as “strong” (Grade 1) or “weak” (Grade 2) based upon the balance between the benefits and risks, burden and cost. The quality or level of evidence is designated as high (Grade A), moderate (Grade B), low (Grade C) or very low (D) depending on factors such as study design, directness of evidence and consistency of results. Grades of recommendation and quality of evidence may range from 1A to 2D.

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Summary of main recommendations

Pre-transplantation

The risk of recurrence should be assessed based on genetic screening, presence of autoantibodies and previous transplant history (1C)

Patients with high or medium risk of recurrence should be offered prophylactic Eculizumab treatment (1C)

Patients at low risk should be warned of the risk of recurrence and monitored closely (2C)

Treatment

Recommendation: Adult patients should receive a single dose of 900mg Eculizumab which is completed prior to the start of surgery. The dose and dosing schedule should be adjusted for body weight in children as per paediatric dosing schedule (1B)

Recommendation: Adult patients should receive 3 further doses of 900mg of Eculizumab at weekly intervals. A dose of 1200mg is administered one week after the final dose of 900mg and every 2 weeks thereafter The dose and dosing schedule should be adjusted for body weight in children as per paediatric dosing schedule (1B)

A further dose of Eculizumab should be considered if there is significant blood loss requiring FFP (2C)

Treatment with Eculizumab should continue unless withdrawn with close monitoring as part of a clinical study (1B)

Patients should receive a Tacrolimus based immunosuppressive regime. The use of anti-IL2 receptor blocking antibody, anti-proliferative agent and steroids should be as per local protocols (2B)

Rapamycin should be avoided post-transplant in patients at risk of recurrent aHUS (2B)

Pre-transplant plasma exchange is not required in patients with aHUS prior to transplantation when Eculizumab is being used (2C)

All patients with aHUS who are being assessed for kidney transplantation should be immunised with tetravalent meningococcal vaccine. Prophylactic antibiotics to reduce the risk of meningococcal infection should be given for the duration of treatment with Eculizumab (1B)

There is a relative contraindication with respect to living related donation but this can be considered in certain circumstances (2C)

The possibility of liver transplantation should be discussed with all patients considering transplantation but is not the recommended option for most patients (1C)

DRAFT

Background

Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy (thrombocytopenia and microangiopathic haemolytic anaemia) characteristically affecting the kidneys, although other organ involvement is recognised. Most commonly (90%) it is caused by infection with a Shiga toxin producing enteric infection, usually *Escherichia coli*. This is a self-limiting disease with a good prognosis in the majority of cases, long term renal failure being a rare sequela. Atypical HUS (aHUS) accounts for the remaining 10% of cases. In the majority of patients (70%) there is evidence of either a genetic or acquired defect in control of the alternative pathway of complement activation. In contrast to the typical, shiga toxin-associated form of HUS the prognosis of atypical HUS is poor. Fifty percent of patients either die or develop renal failure within 1 year of the initial diagnosis of a HUS despite treatment with plasma-based treatment protocols.

With over 50% of patients with aHUS developing end stage renal disease(1), many in childhood or early adulthood, the option of kidney transplantation has to be considered. However, there is a high risk of aHUS recurrence after transplantation with 60% of patients developing recurrent disease, 90% of whom will lose their graft as a consequence of recurrence(2). In patients with mutations in Factor H and Factor I, two commonly affected genes, recurrence occurs in 70-80% of cases post-transplantation. In this patient group when aHUS recurs it almost invariably leads to transplant failure (80-90% of cases). This observation has led to the British Transplant Society recommendation that kidney transplant alone should not be considered for patients with either a Factor H or Factor I mutation(3).

Because mutations in other genes and acquired defects are rare less data is available about the risk of recurrent disease post transplantation. However, the available evidence would suggest that there is a significant risk of recurrent aHUS in patients with mutations in C3 and FB mutations (60% and 100% respectively) with a high risk of graft failure if recurrence occurs(2, 4). The exception is for patients with mutations in Membrane Cofactor Protein (MCP, CD46). This is expressed on endothelial cells and therefore transplantation will restore normal renal endothelial MCP function. Recurrent aHUS has been reported in 2 of 12 transplants in 10 patients with mutations in MCP(5), possibly due to re-endothelialisation of the graft with recipient endothelial cells. In acquired disease related to autoantibodies to complement regulatory proteins, usually Factor H, aHUS recurred in only 1 of 5 patients(4).

Data on the rate of recurrent aHUS after transplant in patients with mutations not affecting complement regulatory genes or with no identified mutation is sparse. One patient with a mutation in thrombomodulin has been transplanted and developed recurrent disease which caused graft failure(6). Despite screening of all genes known to be associated with aHUS mutations are only found in 50-60% of patients and autoantibodies (primarily anti-FH) in a further 5-10% of cases. It is not possible to accurately predict the risk of recurrent disease in individual patients in whom no cause for aHUS is found, but overall the risk is lower (approximately 30%) (7).

Recurrent disease develops early with 60% of cases occurring in the first month after transplantation(2). The higher risk of recurrence during this period may relate to endothelial activation from other causes including ischaemia-reperfusion injury, drugs (particularly calcineurin inhibitors (CNI)), infection and alloimmune responses including the effect of donor specific antibodies. Although early recurrence is most frequent, late recurrence, up to several years after transplantation, has been reported.

Most complement proteins implicated in the pathogenesis of aHUS, with the exception of MCP are synthesised in the liver. Therefore kidney transplantation alone

will not correct the defect in complement regulation. However, combined liver kidney transplantation will correct the complement abnormality and can provide an alternative to long-term complement inhibition to prevent recurrence of aHUS(8).

Eculizumab treatment for aHUS

Eculizumab is a fully humanized anti-C5 monoclonal antibody. It has been licenced for the treatment of paroxysmal nocturnal haemoglobinuria in the UK since 2002 and was licenced for the treatment of aHUS in 2012. To date (2013) 24 cases of Eculizumab use in patients with aHUS have reported (9), including disease in native kidneys (10-12)or recurrence following transplantation(13-16). The results of two trials have been presented (REF in press). Both trials were single arm interventional studies in adolescent and adult patients with aHUS. The first was in 17 patients with aHUS that was resistant to treatment with plasma therapy. There was rapid and sustained haematological normalisation in 87% of patients (15/17) with a fall in serum creatinine of >25% in the majority of patients (11/17). In this study 5 of 6 patients who were dialysis dependent prior to inclusion in the study became dialysis independent following treatment.The second study was in patients responsive to plasma therapy but requiring maintenance plasma therapy to maintain remission (n=20). There was no evidence of increased disease activity in patients when plasma therapy was replaced by Eculizumab. In both studies approximately 25% of patients had no identified mutation in a complement regulatory gene. The response to treatment with Eculizumab was equivalent irrespective of the presence of a complement gene mutation, consistent with the data from previous case reports (9).

In the first trial 7 patients (41%) and in the second 8 patients (40%) had recurrence of the disease in a kidney transplant. Eculizumab was effective in patients with a kidney transplant with similar response rates, again indicating that it is an effective treatment for recurrent disease. This is consistent with previously published case reports.

Pre-emptive use of Eculizumab in renal transplant recipients

There are 9 reported cases of the pre-emptive use of Eculizumab to prevent recurrence of aHUS after transplant(17-21). Eight recipients received a kidney from a deceased donor, and one from a living unrelated donor. These reports are primarily in paediatric patients (median age at the time of transplant 9 years), although 3 patients were aged 18 years or older. Five patients had heterozygous mutations in *Factor H*, 3 genomic re-organisations in *FH/FHR* genes and 1 patient had a gain of function mutation in *C3*. Three patients had received a previous transplant, two of whom had donor specific antibodies with low titre (MFI <1000).

Eight of the 9 patients had a successful transplant without recurrence of aHUS (median follow up 14.5 months, range 2-39 months). One graft was lost due to immediate arterial thrombosis. CH50 activity at the time of thrombosis was undetectable and therefore it was proposed that the arterial thrombosis was unlikely to be related to aHUS. This would suggest that prophylactic treatment with Eculizumab is effective in preventing recurrent aHUS (17).

Patient Selection

The risk of recurrent disease varies depending on the defect that led to aHUS. Eculizumab is expensive and treatment may be long-term, perhaps required for the whole time that the transplant is functioning. Therefore, prophylactic treatment should be targeted at those patients with significant risk of recurrence. High risk of recurrence is reported in patients with FH, FI, C3 and FB mutations.

The prophylactic use of Eculizumab has only been reported in patients with *FH* or *C3* mutations or gene re-arrangements involving FH and FH-related genes. The other mutations in complement proteins lead to similar dysregulation of the alternative pathway. Eculizumab is effective in treating aHUS in patients with non-FH mutations; therefore it is predicted that Eculizumab will prevent recurrence of aHUS post-transplantation irrespective of mutation status. Patients with no identifiable mutation have been shown to respond to Eculizumab treatment in case reports (12, 13, 22) and in the two trials (REF). This group should also be considered for treatment.

The risk of recurrent aHUS and the protective effect of Eculizumab is less predictable in patients in whom no genetic or acquired abnormality is found. Recurrence does occur in patients in the absence of an identified abnormality and therefore these patients have to be considered at medium risk of recurrence. In the trials of Eculizumab no mutation was identified in 25% of patients. The response to Eculizumab was independent of mutation status. It is therefore assumed that Eculizumab will also be effective in preventing recurrent aHUS in patients without an identified mutation.

The risk of recurrence can be stratified (based on (9)):

1. High risk of recurrence:

    Mutations in Factor H or gene re-arrangements involving Factor H and Factor H related proteins

    Gain of function mutations in Factor B or C3

    Loss of previous transplant due to recurrent aHUS

2. Medium risk of recurrence

    No identified mutation or autoantibody

    Mutations in Factor I

    Mutation of uncertain functional significance

    Detectable autoantibodies against FH (significance of other specificities is less clear)

3. Low risk of recurrence

    Mutation in Membrane Cofactor Protein (CD46)

    Previous autoantibody positivity

Recommendation: The risk of recurrence should be assessed based on genetic screening, presence of autoantibodies and previous transplant history.

1C

Patients with high or medium risk of recurrence should be offered prophylactic Eculizumab treatment.

1C

Patients at low risk should be warned of the risk of recurrence and monitored closely.

2C

Eculizumab treatment protocol

Prophylactic Eculizumab has been used in 9 patients to prevent recurrence of aHUS. Various treatment protocols were used (summarised in (REF Zuber). These can be divided into 3 groups:

1. Plasma exchange immediately post-transplant, switching to Eculizumab 5-10 days later (2 cases).
2. Eculizumab starting pre-transplant with living donation or urgent listing for transplantation (2 cases)
3. Dosing with Eculizumab in the 24 hour period immediately prior to transplantation (5 cases).

The three strategies all led to a successful outcome (the graft loss was in a patient dosed within 24hours of transplant – strategy 3). Dosing with Eculizumab prior to transplantation is the simplest protocol to deliver and has therefore been adopted. TMA could develop immediately after reperfusion. Therefore the infusion should be completed prior to the start of surgery.

The 5 cases that received Eculizumab immediately prior to surgery all received a second dose within 24 hours of the first dose, one patient receiving both doses prior to surgery. The rationale for the second dose was to circumvent the concern about high complement activation triggered by ischaemia reperfusion. This is based on the following:

1. Reports of alternative pathway activation during reperfusion of transplanted livers, particularly in patients transplanted because of aHUS (23).
2. Use of a second dose of Eculizumab to prevent complement activation in patients undergoing renal transplantation for castatrophicantiphospholipid antibody syndrome (24).
3. Use of a second dose of Eculizumab in protocols to prevent acute humoral rejection post transplantation (25).

In the clinical studies of Eculizumab haemolytic activity was effectively inhibited by the first dose of Eculizumab. Therefore, even in the context of alternative pathway activation during reperfusion, the generation of C5a and C5b-9 should not occur after a single dose of Eculizumab. There is currently no evidence to support the use of a second dose of Eculizumab in this context. Monitoring of haemolytic activity will determine whether additional early dosing is required.

Significant blood loss may lead to a reduction in Eculizumab efficacy. Therefore, the dose of Eculizumab should be repeated if the transplant recipient requires 4 or more units of blood or FFP at any stage in the first week following transplantation.

In the two studies of Eculizumab for the treatment of aHUS adults were dosed with 900mg weekly for the first 4 weeks and with 1200mg every 2 weeks thereafter. This dosing schedule was effective in maintaining remission. This is the best evidence available for an effective maintenance treatment regime although not specifically applied to prophylactic treatment. Increasing the time between doses to three weeks led to detectable haemolytic activity.

Patients who are being considered for transplantation and who are already on Eculizumab should have their treatment intensified for the first 4 weeks as per protocol. There is a suggestion that complement inhibition may be more difficult to

achieve in the immediate post-transplant period, therefore requiring more frequent dosing.

Recommendation: Adult patients should receive a single dose of 900mg Eculizumab which is completed prior to the start of surgery. The dose and dosing schedule should be adjusted for body weight in children as per paediatric dosing schedule.

1B

Recommendation: Adult patients should receive 3 further doses of 900mg of Eculizumab at weekly intervals. A dose of 1200mg is administered one week after the final dose of 900mg and every 2 weeks thereafter The dose and dosing schedule should be adjusted for body weight in children as per paediatric dosing schedule.

1B

Recommendation: A further dose of Eculizumab should be considered if there is significant blood loss requiring FFP..

2C

Paediatric dosing schedule

Patient body weight 40 kg or more

Initial dose: 900 mg via 35 minute IV infusion then every 7 days for the first 4 doses, followed by 1200 mg for the fifth dose 7 days later.
Maintenance dose: 1200 mg via 35 minute IV infusion every 14 days.

Patient body weight 30 kg to less than 40 kg

Initial dose: 600 mg via 35 minute IV infusion repeated after 7 days then followed by 900 mg for the third dose 7 days later.
Maintenance dose: 900 mg via 35 minute IV infusion every 14 days.

Patient body weight 20 kg to less than 30 kg

Initial dose: 600 mg via 35 minute IV infusion repeated after 7 days then followed by 600 mg for the third dose 7 days later.
Maintenance dose: 600 mg via 35 minute IV infusion every 14 days.

Patient body weight 10 kg to less than 20 kg

Initial dose: 600 mg via 35 minute IV infusion once, followed by 300 mg for the second dose 7 days later.
Maintenance dose: 300 mg via 35 minute IV infusion every 14 days.

Patient body weight 5 kg to less than 10 kg

Initial dose: 300 mg via 35 minute IV infusion once, followed by 300 mg for the second dose 7 days later.
Maintenance dose: 300 mg via 35 minute IV infusion every 21 days.

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Duration of treatment

Eculizumab is approved in Europe for the long-term (life-long) treatment of aHUS. There is limited data about withdrawal of treatment, however it is clear that single doses of Eculizumab are ineffective and discontinuing Eculizumab is associated with a risk of relapse. All patients who enrolled in the two Eculizumab studies were offered the opportunity to continue in an extension of the study. The majority of patients continued on Eculizumab. Recurrence of disease was reported in a proportion of patients who did not continue on treatment. There is insufficient data to stratify the risk of recurrence if treatment is stopped. However there are some mutations associated with severe disease that are likely to be associated with a high risk of recurrence if treatment is discontinued.

The majority of aHUS recurrences occur in the first 3 months after transplantation although recurrences have been reported years after transplantation. Treatment with Eculizumab for 6 months post transplantation would prevent early recurrence but discontinuation would be associated with risk of recurrence. Discontinuation of treatment should only be considered as part of a clinical study with close patient monitoring to detect early evidence of recurrence.

Recommendation: Treatment with Eculizumab should continue unless withdrawn with close monitoring as part of clinical study.

1B

Post-transplant immunosupression

Treatment with both Cyclosporine and Tacrolimus is associated with de novo thrombotic microangioapathy in kidney transplants, the risk being higher with Cyclosporine treatment (up to 14% of patients in one series (26)). It is also evident that the mTOR inhibitor Rapamycin is associated with post-transplant TMA and early use of Rapamycin is an independent risk factor for the development of TMA (27).

D*e novo* post-transplant TMA can develop in the absence of previous aHUS or any known susceptibility factor for aHUS. However, the relationship between aHUS and *de novo* TMA in transplanted kidneys is complex. Approximately 30% of patients who develop *de novo* post-transplant TMA carry mutations in complement regulatory proteins (28) and the *de novo* TMA in these patients is aHUS.

The relationship between de novo TMA, aHUS and immunosuppressive drugs has been extensively studied. There is conflicting data as to whether the post-transplant immunosuppressive regime influences the risk of recurrent aHUS. A small study (17 patients) suggested that the early use of Cyclosporine increased the risk of recurrent aHUS in adults (29). However, this was not confirmed in a larger registry study of 68 paediatric patients with HUS which found no association between cyclosporine and recurrent disease (30). The use of either Tacrolimus or Cyclosporine is not associated with higher risk of TMA (7, 27)and avoidance of CNI treatment did not reduce the risk of recurrent aHUS (2).

In the absence of evidence that CNI usage increases the risk of recurrent aHUS and the definite advantage in reducing rejection with their use, these drugs should be used post-transplantation. Tacrolimus is recommended due to the lower rate of post transplant TMA reported with Tacrolimus and its increased efficacy in preventing rejection.

Evidence for the use or avoidance of specific induction therapies, anti-proliferative drug and steroids is lacking. Treatment should follow local protocols.

Recommendation: Patients should receive a Tacrolimus based immunosuppressive regime. The use of anti-IL2 receptor blocking antibody, anti-proliferative agent and steroids should be as per local protocols.

2B

Recommendation: Rapamycin should be avoided post transplant in patients at risk of recurrent aHUS.

2B

Plasma exchange

Plasma-based therapy (exchange or infusion) has been the only effective treatment for aHUS prior to the introduction of Eculizumab. The rationale for plasma therapy is that defective complement regulators are being replaced and with plasma exchange defective protein removed (in case of a dominant negative effect). Plasma exchange has also been used in regimes to prevent recurrence of aHUS. In the 9 cases reviewed by Zuber et al. 4 patients received plasma exchange as induction treatment (17). The regime for administration of plasma exchange was different in each case. Two patients received plasma exchange post-operatively delaying the first administration of Ecullizumab for 5 (17) and 10 days (19). There was no difference in the outcome of patients whether or not plasma exchange was included in the induction regime.

Recommendation: Pre-transplant plasma exchange is not required in patients with aHUS prior to transplantation when Eculizumab is being used.

2C

Prevention of Meningococcal disease

Complement inhibition increases the risk of infection with *Neisseria meningitidis*. It is therefore recommended that patients are vaccinated with the tetravalent meningococcal vaccine. This vaccine does not generate immunity against serotype B of meningococcus which is common in the UK (ACWY serotypes only). In addition, the effect of post-transplant immunosuppression on immunity against meningococcus is unknown. Antibiotic prophylaxis against meningococcal is recommended for patients on maintenance Eculizumab for PNH (penicillin V 500mg bd or Erythromycin 500mg bd in patients who are intolerant of penicillin) and this is also our policy for aHUS patients..Antibiotics were given to 8 of the 9 patients who who so far have received pre-emptive Eculizumab to prevent recurrent aHUS (17). In view of the severity of meningococcal infection and the immunosuppression post kidney transplant, antibiotic prophylaxis during the treatment period should be given.

Recommendation: All patients with aHUS who are being assessed for kidney transplantation should be immunised with tetravalent meningococcal vaccine. Prophylactic antibiotics to reduce the risk of meningococcal infection should be given for the duration of treatment with Eculizumab.

1B

Monitoring of patients

There is limited data on the use of Eculizumab during transplantation in patients with aHUS. Effective suppression of complement and TMA activity should be monitored. A system to provide non-standard tests will be developed.

1. Haemolytic activity will be measured regulary following transplantation in the first cohort of patients (ideally daily in the first week). This will determine whether a second dose of Eculizumab is required in the early post transplant period.
2. Haemolytic activity, circulating C5b-9, C5a and total C3 will be measured prior to dosing with Eculizumab to confirm adequate complement inhibition. This will be tested prior to each dose of Eculizumab in the first 8 weeks after transplantation Thereafter haemolytic activity, C5b-9 and C5a will be measured every 2 months.
3. Haemoglobin, platelet count, LDH will be measured daily whilst an inpatient and at subsequent clinic visits.
4. A blood film will be performed and haptoglobin concentration measured prior to each dose of Eculizumab in the first 8 weeks after transplantation and 2 monthly thereafter.

Protocol biopsy

A protocol biopsy to look for the presence of sub-clinical TMA is recommended at 3 months after transplantation. Sections from these biopsies should be available for review. Biopsies for clinical indications will be performed as per local protocols.

Pharmacy and dispensing of Eculizumab

The following factors should be considered:

1. The date of a living donor transplant is known several weeks before the surgery. Therefore Eculizumab can be available in hospital pharmacies for administration prior to surgery.
2. The date and time of a cadaveric transplant is not predictable. In addition, there is a narrow time window to administer the Eculizumab prior to the start of surgery to minimise the graft cold ischaemic time. Accessing Eculizumab from a centralised source could lead to an unacceptable delay in the transplant procedure and not be possible outside standard working hours. Therefore Eculizumab will have to be stored in the pharmacies of all renal transplant units who have a patient with aHUS active on the cadaveric waiting list. Sufficient Eculizumab should be available for the administration of the first 2 doses. The Eculizumab may not be used and therefore the drug should be replaced to allow for planned use of older stock at other centres.

Living related Transplantation

The inherited basis of most cases of aHUS increases the risk of disease in family members of affected individuals. There are 4 reported cases of *de novo* HUS in developing in related donors one year of donation(31-33) with disease possibly precipitated by donation.

If the mutation that led to aHUS is known then it is possible to screen for this mutation in the potential living related donor. Identification of the same disease causing mutation in the potential donor is an absolute contraindication to donation.

If the prospective donor does not carry the mutation identified in the recipient other genes should be screened for a mutation or single nucleotide polymorphism haplotype predisposing to aHUS. If no mutation is found the donation could be considered with counselling about the risk of developing aHUS after donation.

If no mutation (or acquired defect) is identified in the recipient then related donors should not be considered because of the risk of an unidentified mutation in family members.

Recommendation: There is a relative contraindication with respect to living related donation but this can be considered in certain circumstances.

2C

Transplanting sensitised patients

There are reports of the use of Eculizumab to treat acute antibody mediated rejection. In addition Eculizumab has been used as prophylaxis against AMR in patients with donor specific antibodies with encouraging results. This indication for Eculizumab is now being assessed as part of a clinical study. It may be possible to transplant selected patients with aHUS who also have donor specific antibodies under cover with Eculizumab. A different Eculizumab dosing schedule is used for transplantation of sensitised patients compared with treatment of aHUS but the cumulative dose in the first 4 weeks is identical as is the dosing schedule after this period. If transplantation is being considered for joint indications two doses of Eculizumab should be administered as per the Mayo clinic protocol on days 0 and 1. However, weekly doses thereafter should be 900mg as per the aHUS protocol.

Combined Liver and Kidney Transplantation

With the exception of MCP, the complement proteins implicated in the pathogenesis of aHUS (FH, FI, C3 and FB) are synthesised in the liver. Therefore liver transplantation in patients with mutations in one of these genes will restore normal complement control. Therefore either liver transplantation (in patients with preserved renal function) or combined liver kidney/transplantation is a potential treatment for aHUS.

The initial experience of liver transplantation in this patient group was not favourable. However more recent reports using prophylactic plasma exchange prior to surgery have reported good outcomes. The requirement for long-term treatment with Eculizumab, in terms of both acceptability and cost, has to be weighed against the mortality associated with liver or dual organ transplantation. In this patient group an alternative to liver transplantation is available. Therefore, the limited supply of liver donors to the waiting list population should also be considered.

Recommendation: The possibility of liver transplantation should be discussed with all patients considering transplantation but is not the recommended option for most patients

1C

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