NEW TREATMENT OPTIONS IN PRIMARY GLOMERULONEPHRITIS

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Summary

Primary Glomerulonephritis (GN) is a heterogeneous group of diseases. Steroids and Immunosuppressives are the mainstay of treatment of this group. The 2012 Kidney Disease Improving Global Outcome (KDIGO) guideline for GN recommends the best evidence based guidelines for GN. After the guideline has been published some of the advances has been seen in some of the trials regarding the use of Rituximab particularly in steroid and Calcineurin (CNI) dependent Minimal change Nephrotic Syndrome(MCNS) and Idiopathic Membranous Nephropathy (IMN). Recently a new entity "C_3 glomerulonephritis" has been proposed for which complement directed therapy (Eculizumab) has been suggested. In some recent trials Abatacept has been used in Focal segmental Glomerulosclerosis (FSGS) and Ofatumumab has been used in Rituximab resistant nephrotic syndrome. In our review we will focus on some of key recommendations of KDIGO guideline along with some of the findings made after the guideline has been published.

Key words

Kidney Disease Improving Global Outcome (KDIGO); Rituximab; C_3 Glomerulonephritis; Abatacept.

Introduction

Glomerulonephritis (GN) is the most common cause of end stage renal disease (ESRD) in developing world. IgA nephropathy is the commonest GN through out the world [1] . Since most of the GN has both remission and relapse and some have spontaneous resolution of certain percentage, treatment of GN has gone through a lot of variations over ages. Responds to treatment is important as it will curtail the cost of dialysis or renal transplantation. Recently published the kidney disease improving global outcomes (KDIGO) clinical practice guideline is a complete evidence based guideline. After its publication trials with newer drugs like Rituximab, Abatacept and different anti compliment antibody were tried in different populations with non homogenous results. This review article will focus on recent treatment update of primary GN as per the KDIGO guideline and trials taken after wards [2].

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Search strategy

Electronic databases from 1994- june 2014 using pubmed and google scholar were searched for text wards 'glomerulonephritis', 'steroid sensitive nephrotic syndrome', 'steroid resistant nephrotric syndrome', 'minimal change disease', 'focal segmental glomerulosclerosis', 'idiopathic membranous nephropathy', 'IgA nephropathy' and 'idiopathic membranoproliferative gn' combined with MeSH terms. The individual topics were reviewed along with their available references. Salient features of KDIGO guideline were reviewed in toto as baseline evidence.

Discussion

Minimal Change Disease (MCD)

Till today the treatment protocol of Initial episode of steroid sensitive nephrotic syndrome (SSNS) in children remains same like originally prescribed by international study of kidney disease in children (ISKDC) [2]. Steroid mono therapy with daily steroid up to 6weeks followed by alternate day therapy for two to five months with tapering of the dose is the time-honored treatment protocol. In case of adult no alternate day therapy rather dose is continued daily for minimum 4 weeks to maximum 16 weeks and after complete remission (proteinuria up to 300mg/d)steroid is tapered slowly by 5-10mg per week over a period of 6 months [3] . In case of infrequent relapse in children the dose of steroid is changed into alternate day when urine dipstick is <1+ for three consecutive days and continued for 4 weeks and stopped without tapering. In case of adult there is no alternate day therapy and up to 3 relapses a year can be treated with steroids as initial therapy. In case of contraindication (uncontrolled DM, severe osteoporosis and psychosis) or intolerance to steroid even in initial episode Cyclophosphamide (CYC) or Calcineurin inhibitor (CNI) may be used in adults.

In case of frequent relapsing (FR) and steroid dependent (SD) SSNS in children still steroid is used but alternate day therapy for at least 3 months, sometimes changing to daily prednisolone during infections (Fig 1). Then alternate day therapy is reduced and maintained at lowest possible dose (o.48mg/kg EAD or 0.25 mg/kg daily) even (for 9 to 18 months [4]. It there is steroid related adverse effects CYC (2mg/kg/day for 8 to 12 weeks) or Chlorambucil (0.1 to 0.2mg/kg/day for 8 week) is tried after remission with steroids and along with these alkylating agents EAD Prednisolone (1.5mg/kg for 4 weeks, 1 mg/kg for next 4 weeks, then tapered over next 2/3 months) is given [5]. Indian group of nephrologists tried Levamisole (2.5mg/kg on EAD for 12 months) with Prednisolone (1.5mg/kg EAD for 4 weeks, then dose is gradually reduced by 25mg/kg every 4weeks to a maintenance dose of 0.5mg/kg for 6 months [6]. They recommended alkylating agent when Levamisole is failed [7] .

KDIGO recommended CNI cyclosporine (CIC) (4-5mg/kg/day in two divided doses) or Tacrolimus (TAC) (0.1mg/kg/day in two divided doses) or Mycophenolate mofetil (MMF) (1200 mg/m^2/day in two divided doses for at least 12 months as steroid sparing [8]. Indian group of pediatrician recommended CNI only when patients do not benefit from CYC and MMF. Along with CIC/TAC/MMF prednisolone is given like given along with Levamisole.

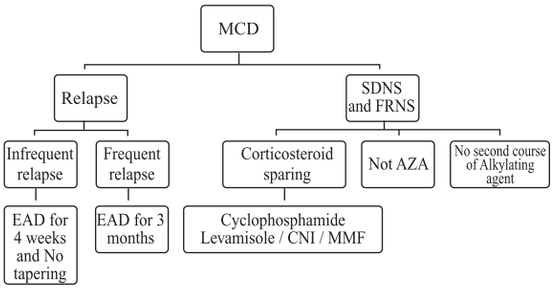

Fig 1 : MCD relapse and SD NS in children

In the frequent relapser (FR) / steroid dependant (SD) MCD adult patient oral CYC 2–2.5 mg/kg/d for 8 weeks is tried first. CNI (CIC 3–5 mg/kg/d or TAC 0.05–0.1 mg/kg/d in divided doses) for 1–2 years for patients with FR/SD MCD who relapsed despite CYC, or to avoid gonadal toxicity.MMF 500–1000 mg twice daily for 1–2 years for patients intolerant of corticosteroids, CYC, and CNIs is used. (Fig 2). The addition of steroid to CYC added no benefit in adult [9]. But addition of prednisolone (1mg/kg/day, reducing 10mgevery 4 weeks to reach 10mg/d which is continued upto end of 6 months) to CIC causes sooner remission [10]. Corticosteroid resistant MCD in adult is due to undetected FSGS which needs further biopsy.

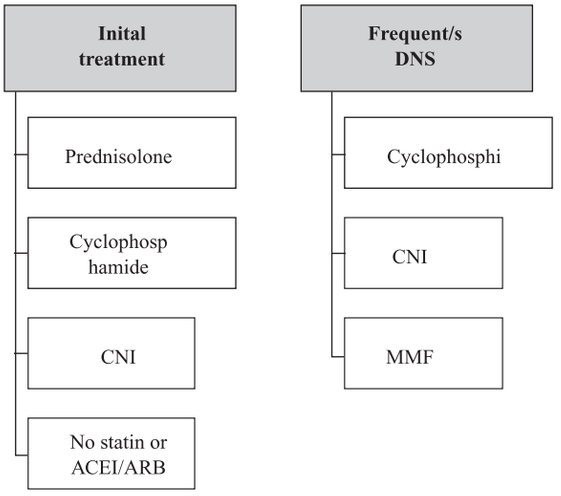

Fig 2 : MCD in adult

In children Azathioprine (AZA) is not proposed as corticosteroid sparing agent.
Rituximab 375mg/m^2/week for 4 weeks in SD SSNS is tried in 22 patients who showed 86% reduction in maintainence immunosuppression [11].
Rituximab causes remission of proteinuria in 6 out of 9 steroid-CNI dependent paediatric patients at least for 12 months with no immunosuppressive(IS) for last half of one year[12].
Rituximab also achieved remission in upto 80% of steroid sensitive 54 children when it was combined with low dose steroid and TC [13].

Randomized Control Trial (RCT) is needed for role of Rituximab, Levamisole in FR/SD MCD in adult.
In children in Steroid resistant nephrotic syndrome(SRNS) CNI with low dose steroid is tried first , if partial or complete remission after 6 months it is continued for 12 months and CYC should not be given. If CNI fails MMF with dexamethasone gave a variable result [14,15] . If Relapse after above therapy oral steroid or previous successful immunosuppressive or alternate immunosuppressive is tried considering risk vs benefit. Rituximab for SRNS in children is still not proved by RCT though few small trials showed favourable results [16,17] (Fig 3).

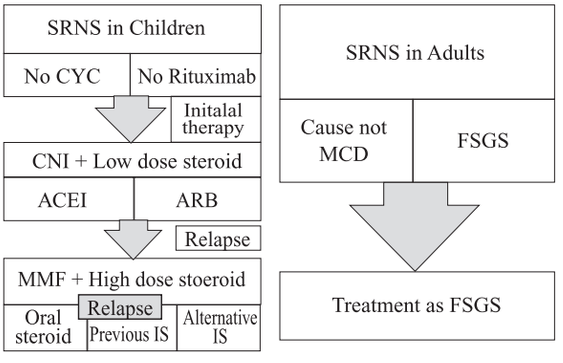

Fig 3 : SRNS

In Initial episode ACEI/ARB and statin are not used. they are used in case of FR / SD NS in adult and SRNS in children.

Rituximab was used safely and repeatedly (1-5 times) in steroid-CNI dependant children in italy and 50% of children can be maintained for 9 months without oral IS in a recent study [18] .

In another study 17 adult patients were treated with rituximab for steroid-dependent minimal change nephrotic syndrome over a mean follow-up of 29.5 months (range 5.1–82 months). Seventeen patients with steroid-dependent or frequently relapsing minimal change nephrotic syndrome, unresponsive to several immunosuppressive medications, were treated with rituximab. Eleven patients had no relapses after rituximab infusion (mean follow-up 26.7 months, range 5.1–82 months) and nine of them were able to come off all other immunosuppressive drugs and steroids during follow-up. Six patients relapsed at least once after a mean time of 11.9 months (mean follow-up 34.5 months, range 16.9–50.1 months), but their immunosuppressive drug treatment could be stopped or markedly reduced during this time. No adverse events were recorded. Thus, rituximab is efficient and safe in adult patients suffering from severe steroid-dependent minimal change disease (Fig 4) [19].

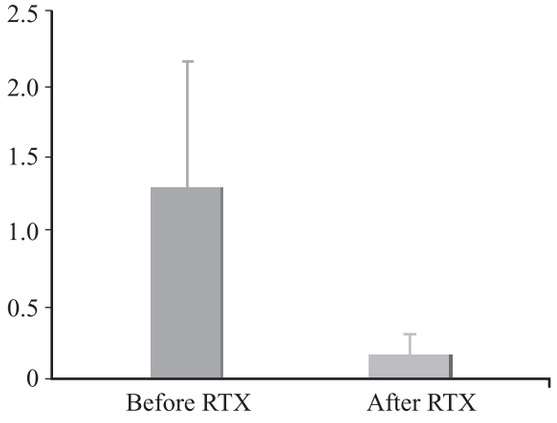

Fig 4 : Rituximab in adult : Studied in France. Out of 17, 11 had no relapse

Ofatumumab, a humanized anti-CD20 monoclonal antibody was used in four case of Rituximab resistant NS. All of them maintained remission for 9 months [20].

Idiopathic Focal Segmental Glomerulosclerosis (FSGS)

The first line therapy is prednisolone or CNI (in case of contraindication or intolerance of steroid) but not CYC. Prednisolone dose is like MCD in children. CNI is also same as MCD but prednisolone is combined as 0.15 mg/kg/d for 4-6 months and then tapered off over 4-8 weeks. In SR FSGS steroid is tapered off over 6 weeks and CNI is started. Role of AZA, Rituximab or MMF with high dose dexamethasone is debatable[21,22]. Relapse of FSGS is treated like relapsing MCD.

Plasma exchange has a role in recurrent FSGS in renal allograft but its role in primary FSGS is not established. Antifibrotic agent pirfenidone has some benefit in a trial [23] . Recently a fusion protein Abatacept has been tried in 5 FSGS patients with complete or partial remission of proteinuria (Fig 5) [24].

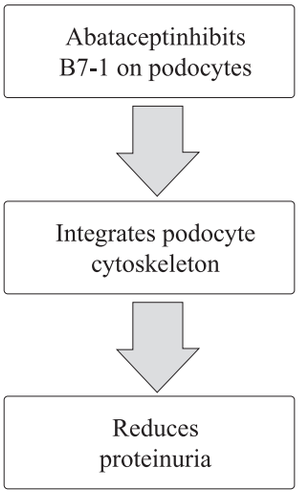

Fig 5 : Abatacept in FSGS

Idiopathic Membranous Nephropathy (IMN)

It is NS of adults. Only 3% of childhood NS is IMN. IMN in 80% clinically presents as NS and in 20% it is subnephrotic .Spontaneous complete remission occurs in 20% and spontaneous partial remission ensues in 15-20%. About 15-30% suffer relapses. Initial therapy be started only in patients with nephrotic syndrome AND when at least one of the following conditions is met : i)Urinary protein excretion persistently >4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy during an observation period of at least 6 months .ii)The presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome iii)Serum creatinine has risen by 30% or more within 6 to 12 months from the time of diagnosis but the e.GFR is not less than 25–30 ml/min/1.73 m^2 [25].

Initial therapy consists of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents("Ponticelli regime"). Cyclosporine or tacrolimus can be used for a period of at least 6 months in patients who meet the criteria for initial therapy, but who refuse or have contraindications to the cyclical corticosteroid/alkylating-agent regimen (Fig 6).

The dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, if remission is maintained and there is no CNI-related nephrotoxicity, it is continued for at least 12 months. Patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure.

Corticosteroid monotherapy or MMF monotherapy should not be used. However MMF with steroid gives equal result in some study though relapse rate is high [2]. Continuous daily use of alkylating agent is effective but risk of toxicity if used >6 months. Due to lack of RCT no specific recommendation is made for Rituximab or long acting ACTH (1-2 mg/week im for1yr.).Azathiaprine does not favourably influence the course. Unresponsiveness to initial therapy occurs in 10-30%. IS therapy should not be used if SCr persistently >3.5mg% or kidney size less than 8cm.

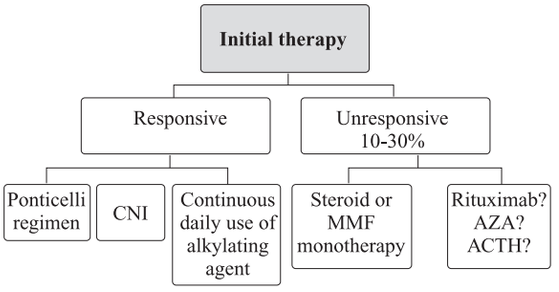

Fig 6 : IMN

Patients with IMN resistant to alkylating agent/steroid-based initial therapy can be treated with a CNI .Patients with IMN resistant to CNI-based initial therapy can be treated with an alkylating agent/steroid-based therapy.

Relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. If a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy , the regimen be repeated only once for treatment of a relapse. Rituximab has been chosen as 2nd or 3rd line therapy in relapse cause [26,27,28,29] (Fig 7).

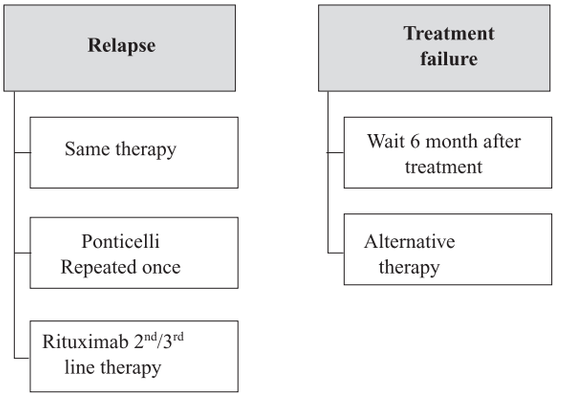

Fig 7 : IMN

Treatment of IMN in children is like adult but Ponticelli should be used only one time.

Phospholipase A2 receptor (PLA2R) has been discovered as the possible target antigen in the development of IMN. Antibodies to PLA_2R are present in up to 80% patients with idiopathic membranous nephropathy.Those with high titres are less likely to enter spontaneous remission. The direct measurement of autoantibodies for PLA2 receptor, which correlates with disease activity and response to therapy, support the diagnosis of 'idiopathic' membranous nephropathy. [30, 31] .

Idiopathic Membranoproliferative Glomerulonephritis (MPGN)

KDIGO suggested Adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function could receive oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy limited to less than 6 months. There are no randomized controlled trials of steroid use in adults with MPGN. Long term alternate steroid therapy in children was suggested by some studies with equivocal results [32,33]. Benefit of combined aspirin and dipyridamole for adults with MPGN was doubtful [34,35]. Some observational studies showed benefit with use of iv steroid combined with CYC or MMF in Rapidly progressive MPGN[36,37] . Role of Rituximab in Type 1 MPGN was described in one study [38].

Immunoglobulin A Nephropathy (IgAN)

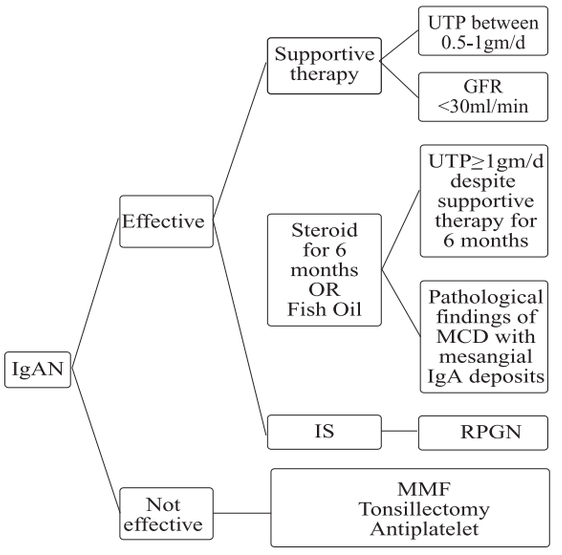

Fig 8: Treatment algorithm of IgAN

Treatment requires exclusion of secondary causes. In IgAN risk of progression is assessed by proteinuria, BP, and GFR at time of Diagnosis. Obesity is an independent risk factor for ESRD (>25kg/m²).

If proteinuria (UTP) does not decrease <1g/d after 3-6 months of ACEI/ARB and eGFR >50ml/min, a 6 month course of steroid is advocated. Fish oil (3.3 g/d) is also advocated in such cases. If GFR < 30ml/min/1.73 mm² no immunosuppressive is used unless crescentic IgAN .MMF is not used in IgAN .Antiplatelet and tonsillectomy are not suggested for IgAN. Treatment of crescentic IgAN is like ANCA vasculitis (prednisolone and cyclophosphamide or rituximab and prednisolone) [39]. IgAN in which mesangial IgA deposits are found along with Pathological features of MCD treatment like MCD is suggested (Fig 8). Recently some trials for IgAN depending on scores of pathological features as evidenced by Oxford –MEST classification is going on (Table 1) [40, 41].

Table 1 : the Oxford classification of IgA nephropathy

Pathological finding	Score		
	0	1	2
M-Mesangial phypercellularity (% of glomeruli)	<50	>50	NA
E-Endocapillary hypercellularity	No	Yes	NA
S-Segmental glomerulosclerosis or adhesion	No	Yes	Na
T-Tubular atrophy and/or interstitial fibrosis (% of biopsy sample)	0-25	26-50	>50

Additional features to be recorded but not part of the score include the number of glomeruli available in the biopsy sample, cellular and fibrocellular crescents (%), necrosis (%of glomeruli) as well as global glomerulosclerosis (% of glomeruli). Abbreviation : NA, not applicable.

There are three large trials (Fig 9): i) Advances in the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA). This multicenter, multinational study supported by the ERA-EDTA Working Group of Immunonephrology will provide information beyond the validation of the Oxford classification of IgAN, aiming at detecting for each lesion the "point of no return" when no treatment is effective [42]. ii) Supportive Versus Immunosuppressive Therapy of Progressive IgA nephropathy (STOP) IgAN trial S [43]. iii) Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING Study) [44].

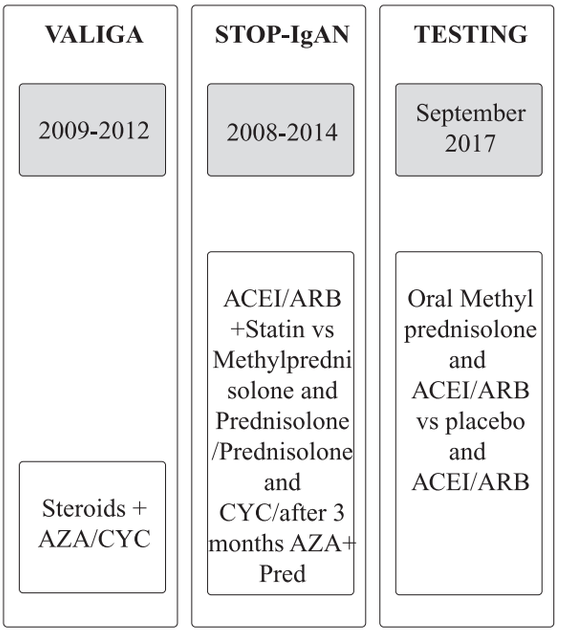

Fig 9 : VALIGA , STOP-IgAN and TESTING trials

C_3 Glomerulonephritis

C_3 Glomerulopathy (Fig 10) is a recently introduced pathological entity whose original definition was glomerular pathology characterized by C3 accumulation with absent or scanty immunoglobulin deposition. C_3 is also predominantly deposited in Dense deposit Disease(DDD) and post-streptococcal GN(PSGN) [45] .Before 2012, treatment has invariably included some type of anti-cellular immune suppression targeting T and/or B cells (e.g., cyclophosphamide, mycophenolate, or rituximab) with or without plasma therapy. More recently, treatment plans have sometimes included anti-complement C5 therapy [46].

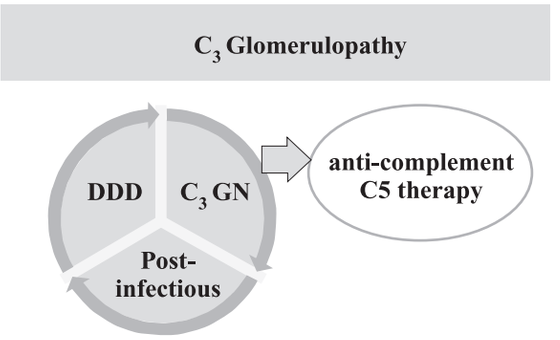

Fig 10 : C_3 Glomerulopathy

Conclusion

Steroid monotherapy is still the treatment of choice in MCD. FSGS and IgAN but steroid monotherapy is not effective in IMN. No role of AZA in MCD and MMF in IgAN was till proved in RCT. Cyclophosphamide or CNI may be initial therapy in adult MCD . CNI may be initial therapy in case of FSGS and CYC is not used in FSGS. Cyclophosphamide is not used in SRNS in children. Steroid resistant MCD in adults is actually not MCD, it is likely to be FSGS.Multiple courses of Rituximab in relapsing MCD and IMN were tried in recent trials.Though in IMN second course of alkylating agent is advised in adult but in MCD alternate therapy is chosen.In IgAN , no other drug besides steroid was found to be more effective in trials.When GFR <30 ml/min, IS drugs are not suggested in IgAN and IMN.Anticomplement therapy is tried in C_3 GN. Fusion protein (Abatacept) is found to be effective in Proteinuric GN. Further prospective multicenter RCT is necessary to recommend the universal therapy for global application.

Disclosure

All the authors declared no competing interest.

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