Chapter 8

Summary, general discussion and suggestions for future research

Summary

Sarcoidosis is a multisystemic disease of unknown cause characterized by cellular immunity activity with formation of noncaseating granuloma in various organ systems.[1,2] Sarcoidosis can affect any organ system, so patients can suffer from a wide spectrum of organ-specific symptoms. In addition to symptoms related to the specific organ involved, patients often have non-specific complaints such as exercise intolerance, general weakness, and fatigue.[2-5] Pharmacological treatment options aim to treat the disease and preserve organ function. Despite effective treatment of their sarcoidosis, many patients continue to experience fatigue and exercise intolerance.[5,6] Exercise training is a generally accepted treatment strategy in chronic lung diseases to reduce physical impairments, dyspnea, and fatigue.[7] However, evidence regarding the benefits of physical training in sarcoidosis is scarce,[8-10] and mostly comes from observational studies with rather small patient populations.

The aims of the studies presented in this thesis were to examine the consequences of sarcoidosis-related problems for patients' lives, and determine relationships between clinical characteristics and sarcoidosis-related problems such as fatigue, limited exercise capacity, and decreased muscle strength. In line with this, we explored the influence of a physical training program on exercise capacity, muscle strength, and most importantly, fatigue. Sarcoidosis patients included in these studies were referred to the former ILD (interstitial lung disease) care team of the Gelderse Vallei Hospital in Ede, The Netherlands. Over a period of 22 months, patients underwent exercise testing and muscle testing and completed questionnaires before and after a physical training program. This was first examined in a pilot study, after which we conducted a two-group observational study. Finally, recommendations regarding physical training in sarcoidosis were drawn up with the help of a systematic literature overview and a survey of expert opinion regarding the use of physical training in sarcoidosis. The present chapter offers an overview of the main findings, as well as practical implications and recommendations for future research.

Overview of the main findings

Chapter 1, the general introduction, provides a summary of the pathogenesis, epidemiology, clinical presentation, and non-organ-specific symptoms of the disease. These non-specific complaints, e.g. fatigue, exercise intolerance, and arthralgia, impose a burden on patients' lives. The roles of both pharmacological and non-pharmacological interventions in the management of sarcoidosis are outlined.

Chapter 2 presents an overview of the literature regarding the wide-ranging consequences of sarcoidosis. In addition to the specific organ-related symptoms, less specific disabling symptoms, including fatigue, exercise intolerance, small fiber neuropathy (SFN), depressive symptoms, anxiety and cognitive impairment, can have a

major influence on the daily activities and the social and professional lives of the patients, resulting in a reduced quality of life (QoL). A multidisciplinary approach is generally recommended by experts for these patients, one that focuses on the somatic as well as psychological aspects of this erratic disorder. As regards pharmacological treatment, glucocorticoids are the cornerstone therapeutic agent and have a favorable short-term effect on functional impairments. Some patients, however, require more aggressive treatment. The decision to start systemic immunosuppressive treatment or not should be based on the patients' symptomatology, including the impact on their QoL, as well as the extent of compromised organ function. Sarcoidosis patients may also benefit from non-pharmacological (additional) treatment options. Developing the most appropriate therapeutic approach for sarcoidosis, including rehabilitation programs, requires consideration of the possible impact of fatigue, SFN symptoms, pain, cognitive functioning, sleep disorders, as well as other relevant aspects of this multisystem disease. Therefore, personalized medicine is key.

Chapter 3 reports on the process of validating King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. The KSQ is a brief questionnaire assessing the health status of patients with sarcoidosis, using five modules (General health status, Lung, Medication, Skin and Eyes). Previously it was only validated in one English sarcoidosis cohort. The KSQ was translated according to international guidelines and tested in interviews with patients. In addition, consecutive outpatients completed multiple questionnaires twice, two weeks apart. Of the 98 patients included, 85 had lung, 22 skin and 24 eye disease. The findings showed good construct validity of the KSQ General Health Status (GHS) module against the World Health Organization Quality of Life-BREF questionnaire. The Medication module correlated weakly to moderately with most questionnaires, including the Fatigue Assessment Scale (FAS) (r=0.39). The correlations with organ-specific questionnaires varied from strong for Eyes (r=0.75) and Skin (r=-0.62) to moderate for Lung (r=-0.45 with the MRC breathlessness scale). The correlations between the KSQ GHS domain (r=0.81) and generic questionnaires (Euroqol-5D-5 level [EQ-5D-5L], Global Rating of Change – Quality of Life [GRC-QoL], and WHOQOL-BREF) were strong, especially for the Energy and Fatigue aspect (r=0.84)). All KSQ modules correlated moderately to strongly with the FAS (r=0.50-0.81). The organ-specific 'Lung' module of the KSQ did not show any relationship with lung function test results, except for a weak correlation with FVC % of predicted (r=0.24). Internal consistency was good for all KSQ modules (Cronbach's α 0.72-0.93). Intraclass correlation coefficients (0.70-0.90) and Bland-Altman plots showed good repeatability of the KSQ. This Dutch KSQ is the first health status questionnaire for sarcoidosis in the Netherlands. Our validation also represents the first non-English validation of the questionnaire. The KSQ is simple to administer, adaptable to individual organ involvement and has proved to be a valid and reliable health status measurement for Dutch patients with sarcoidosis.

Chapter 4 presents the findings of a study into the relationship between fatigue and both exercise capacity and clinical characteristics (age, sex, time since diagnosis,

body mass, lung function tests, and inflammatory markers) in sarcoidosis patients. Additionally, it outlines the predictive value of exercise test results and other relevant clinical characteristics for the independent variable fatigue. All patients underwent exercise testing (six minute walk test [6MWT], the Steep Ramp Test [SRT]) and skeletal muscle function testing (hand grip strength [HGS], chair rise time [CRT], and elbow flexor muscle strength [EFMS]). Fatigue was measured with the FAS in all patients. In total, 146 patients were included in this cohort study. Prevalences of fatigue (77%) and exercise intolerance (75%) were high. Exercise capacity only showed a weak correlation with fatigue (r=0.25, p=0.002 for 6MWD % of predicted; r=0.24, p=0.003 for SRT). Fatigue was not correlated with the demographic variables of age, body mass index, or time since diagnosis. Nor did inflammatory markers, lung function tests, or hand grip strength show any significant correlations with fatigue. Backward multiple regression analysis showed that only female sex (t=-2.614, p=0.01) and 6MWD % of predicted (t=-2.773, p=0.006) were independent predictors of fatigue. However, the r(2) value indicated that these two variables together explained only 11% of the FAS score. In conclusion, this study showed that fatigue and exercise intolerance are substantial problems among sarcoidosis patients. While it is well known that sarcoidosis-related fatigue is multi-factorial in nature, our study failed to discover any meaningful associations based on the available data for this patient sample. Further research to clarify the phenomenon of fatigue in sarcoidosis is important, in order to enhance both medical and allied health care strategies to reduce fatigue.

Chapter 5 addresses the use of a tailored physical training program by patients suffering from idiopathic or end-stage-sarcoidosis-related pulmonary fibrosis. The natural history of disease in patients with stage IV (fibrotic) sarcoidosis may mirror that of patients with idiopathic pulmonary fibrosis (IPF), as both are affected by progressive dyspnea, exercise limitation and fatigue. All 24 patients referred to the ILD care expertise team of the Gelderse Vallei Hospital underwent exercise testing (6MWT, SRT), skeletal muscle function testing (HGS, EFMS), and pulmonary function tests (DLCO, FEV_1, FVC) at baseline and after completion of a 12-week physical training program. At baseline, the percentage of predicted DLCO, FVC, FEV1 and exercise capacity (assessed by six-minute walking distance [6MWD] or maximal oxygen uptake) was reduced in both groups. After program completion, exercise capacity had improved (>10% improvement on 6MWD) in 13 subjects (54.2%): 7 with IPF and 6 with sarcoidosis. Other secondary endpoints, including pulmonary function tests and patient-reported outcome measures, improved in some subjects. A 12-week physical training program improved or maintained exercise capacity in the majority of patients with IPF (despite disease progression) or fibrotic sarcoidosis. The results from this pilot study could be used to design prospective studies aimed at answering lingering questions about exercise training in patients with these progressive, incurable conditions.

Chapter 6 discusses the results of sarcoidosis patients following a physical training program. The aim of the study was to establish whether a physical training program improves exercise capacity and reduces fatigue. At our center, all sarcoidosis patients

were routinely recommended to undergo physical testing at the Department of Physical Therapy. Exercise capacity (6MWT, SRT), skeletal muscle function (HGS, EFMS, CRT), fatigue (FAS) and pulmonary function tests (DLCO, FEV_1, FVC) were applied at baseline and after a 12-week physical training program. Ninety patients underwent baseline testing, 49 of them completed the training program (group I), and 41 chose not to participate (group II). At baseline, there were no between-group differences regarding fatigue, pulmonary function, or exercise capacity. The 6MWD for Group I improved between baseline and 3 months, while the 6MWD remained unchanged in Group II ($F=72.2$, $p<0.001$). Group I showed a significantly larger decrease in fatigue compared with Group II ($F=6.27$, $p=0.014$). Lung function tests did not change in either group. Our findings indicate that a supervised, 12-week, aerobic exercise and strength training program improves exercise performance and strength, and reduces fatigue in patients with sarcoidosis. The results were independent of age, gender, time since diagnosis, baseline pulmonary function (and other markers of sarcoidosis severity), inflammatory status, or pharmacological interventions. We would argue that physical training should be considered as a first-line therapy for patients suffering from sarcoidosis.

Chapter 7 presents a systematic literature overview (phase I) on physical training and pulmonary rehabilitation in patients with sarcoidosis. An extensive search strategy resulted in four publications on this topic. Each study suggested benefits in the areas of exercise capacity, fatigue, and QoL. Although relatively few studies have been done so far, there is encouraging evidence of a positive effect of physical training on the devastating symptoms of sarcoidosis. Our systematic literature review guided an international consensus effort among sarcoidosis experts to establish recommendations for the implementation of exercise as a treatment for patients with various manifestations of sarcoidosis (phases II and III). Most experts were pulmonologists (>82%) and the majority (70%) had more than 10 years of experience with sarcoidosis patients. They considered physical training to be a valuable and safe intervention. Pulmonary involvement, fatigue, and muscular and extra-pulmonary involvement were considered the most important indications for physical training. Almost 50% of the respondents indicated situations where physical training could potentially harm patients, e.g. patients with untreated arrhythmias. Results obtained during phases I and III were assembled to prepare ten recommendations regarding physical training in sarcoidosis. Finally, the recommendations were submitted to a panel of 15 leading international sarcoidosis experts familiar with the subject of exercise in sarcoidosis. Recommendations with an agreement level below 75% were excluded from the final selection. This process resulted in eight key recommendations, regarding indications, standardized assessment, content of physical training program, safety considerations, and monitoring.

General conclusion

Exercise is a well-documented safe and effective intervention for the prevention and rehabilitation of chronic diseases. Sarcoidosis has many faces and many phenotypes, as

well as a wide spectrum of symptoms, including exercise intolerance, muscle weakness, fatigue, and diminished QoL. This justifies tailoring the treatment strategies to the specific needs of individual sarcoidosis patients, including the use of training modalities. In the short term, supervised exercise training programs have demonstrated clinical benefits in improving exercise capacity, fatigue, dyspnea, and QoL in patients with sarcoidosis. An exercise-based rehabilitation program should be offered to all sarcoidosis patients suffering from these problems. Expected outcomes are improvements in muscle strength and endurance, reduction of fatigue and dyspnea, and ultimately improvement of QoL. A thorough patient assessment should be performed at the beginning and end of rehabilitation to evaluate the program outcomes, including assessment of fatigue, dyspnea, muscle strength, and exercise capacity. Addressing these issues in the management of sarcoidosis patients enables clinicians to tailor their therapies. Even more importantly, it helps patients in their struggle with this devastating disease. The available data underscore the importance of implementing training principles to target the pathophysiological impairments due to sarcoidosis, in order to optimize training adoption and enhance the outcomes. The current exercise training data regarding sarcoidosis provide sufficient evidence of clinical benefit to recommend exercise-based pulmonary rehabilitation as a standard of care for sarcoidosis.

General discussion

Sarcoidosis patients often present with complaints specifically related to the organ systems involved. The majority of these patients also suffer from non-specific health complaints, like fatigue, SFN and exercise intolerance. Fatigue in sarcoidosis is a problem which is affected by many different variables. Deconditioning of skeletal muscle plays a key role, although systemic effects of sarcoidosis on muscle have not yet been studied extensively. Fatigue may be explained not only by decreased pulmonary functions and the negative vicious cycle of deconditioning, but also by muscle weakness and exercise intolerance, due to sarcoidosis located in the skeletal muscle itself.[11]

The prevalence and impact of these non-specific complaints was outlined in studies by Marcellis et al.[4,12,13] They also found that these non-specific complaints have a stable and persistent character.[4] These non-specific health complaints correlate poorly with objective clinical parameters (e.g. chest X-ray, pulmonary function tests).[14,15] Patients may suffer from substantial fatigue even in the absence of other symptoms or disease-related abnormalities.[5]

The cause of fatigue in sarcoidosis patients is multifactorial, and fatigue has a great impact on patients' lives, so the evaluation and treatment of sarcoidosis-associated fatigue needs a comprehensive evaluation. Researchers have recommended identifying reversible causes of fatigue related to metabolic disorders (diabetes, thyroid dysfunction, anemia), psychological conditions (depression, anxiety) and organ-related

conditions (SFN, sleep disturbances). Sarcoidosis patients may continue to experience persistent fatigue despite appropriate identification and treatment of these reversible causes. For these patients, neurostimulant therapy may be helpful, as well as cognitive behavioral therapy.[5]

In line with other studies, we found that the level of sarcoidosis-associated fatigue was not explained by lung function test results, nor inflammatory markers or other clinical parameters. In addition, our study found only weak relationships between fatigue and exercise capacity.[12,16] De Kleijn et al. described several significant predictors of fatigue, e.g. cognitive failure, depressive symptoms, symptoms of suspected SFN and dyspnea.[17,16] Cognitive therapy may be indicated to improve coping strategies or stress perception and antidepressants can be considered in patients with a clinical depression.[18,19] Sleeping problems as well as other causes of fatigue should also be evaluated and treated appropriately.[20-25] Sarcoidosis-associated fatigue may either improve or worsen with therapy.[4,22-25] Persistence of fatigue or new-onset fatigue during therapy may be an adverse effect of corticosteroids.[26] Various neuro-stimulants, including methylphenidate and tumor necrosis factor-alpha (TNF-α) inhibitors have been found to be effective for the treatment of sarcoidosis-associated fatigue.[5,18,27-29] These agents and other therapeutic options (e.g. psychological interventions) may be useful for the treatment of this fatigue.[5]

Pharmacological treatment alone may be not sufficient for the treatment of sarcoidosis-associated fatigue and exercise limitations.[5] Several drugs (e.g. corticosteroids) used in the management of sarcoidosis may have adverse effects on exercise capacity and muscle function.[11] Impaired exercise capacity and muscle function will result in further deconditioning and decreasing activity levels of patients.[12,13] To interrupt this vicious circle it is important to be aware of this lack of effect and the negative side effects, and to initiate additional therapies, such as physical training, to restore or improve exercise capacity and muscle function.[13]

Rehabilitation is considered a useful therapeutic option in other chronic diseases (including lung diseases).[30] So far the available studies found significant and clinically relevant clinical benefits regarding exercise capacity, muscle strength, and fatigue.[8-10,31,32]

The reasons why rehabilitation may be effective in treating non-specific sarcoidosis-related complaints has to do with the characteristics of the disease. The main characteristic of sarcoidosis is the formation of granuloma, which is hallmarked by an immune response, releasing chemokines and cytokines (e.g. interferon-ɣ, interleukin (IL)-2, IL-12, IL-18, and TNF-α). This process is suggested to induce persistent inflammation and subsequent tissue damage.[2] Systemic inflammation can be a trigger for oxidative stress, which may contribute to muscle dysfunction in chronic diseases.[33,34] Furthermore, treatments such as corticosteroids may also adversely impact on

muscle function, causing e.g. myopathy, fatigue, and psychological burden, as well as sleeping problems.[19,35,36] In a study among 25 patients with sarcoidosis, only for those patients who received oral corticosteroid treatment (n=11) was the quadriceps peak torque inversely related to the mean daily dose of corticosteroids received in the 6 months before testing.[11]

Physical inactivity leads to the accumulation of visceral fat and consequently to the activation of a network of inflammatory pathways. Chronic inflammation promotes the development of insulin resistance, atherosclerosis, neurodegeneration, and tumor growth,[37,38] and is associated with the development of several diseases.[39,40] Physical activity, or exercise, mediates anti-inflammatory effects via the reduction of visceral fat mass and the establishment of an anti-inflammatory environment with each bout of exercise.[38,41-43] Several studies have shown that muscle fibers express the myokine IL-6 in response to muscle contractions. This IL-6 then exerts its effect both locally within the muscle and, when released into the circulation, in a hormone-like fashion in a number of organs.[41]

The mechanism by which exercise rehabilitation improves outcomes in sarcoidosis is not clearly understood. It is most likely that this type of rehabilitation ameliorates peripheral muscle dysfunction by providing an effective training stimulus to the muscle. It may also improve cardiovascular fitness, improve disease self-management and provide effective psychosocial support.[9,31,32,44] There is no evidence that rehabilitation impacts on the progression of the disease. We showed that exercise capacity (6MWD +70m vs +4m) and muscle strength improved, and fatigue decreased, in 49 patients who attended a physical training program, compared to 41 patients who did not take part in the training program.[32] In line with the information presented above we suggest that physical training (or exercise rehabilitation) is a valuable treatment option, in addition to pharmaceutical treatment strategies, to reduce chronic systemic inflammation, visceral fat, and oxidative stress, thereby improving muscle strength and exercise capacity and reducing sarcoidosis-associated fatigue. These strategies are all intended to improve patients' quality of life and make them feel more comfortable.[45]

Since rehabilitation delivers relevant gains in patient-centered outcomes, it is a treatment recommended for people with ILD by the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines for IPF management and the ATS/ERS pulmonary rehabilitation statement.[46,47]

The suggested indications for initiating physical training in sarcoidosis are broad, but the heterogeneity of manifestations and symptomatology mean that the management of sarcoidosis patients is complex, and indications as well as relative contraindications should be carefully taken into account. Although multi-factorial sarcoidosis-related pulmonary hypertension is a serious concern in severe sarcoidosis, current international guidelines by the ATS and the ERS nevertheless support exercise training within the context of pulmonary rehabilitation for pulmonary arterial hypertension (PAH).[48] Manifestations of pulmonary hypertension and cardiac

involvement should be considered as relative contraindications and caution should be exercised by the qualified supervisors (chapter 7 of this thesis).

Practical implications

As stated above, patients may suffer from all kinds of non-organ-specific symptoms in addition to symptoms specifically related to the organs involved. Since these problems are frequent and may have a major influence on patients' daily activities and their social and professional lives, it is important to recognize and quantify these problems in the evaluation of sarcoidosis patients. We therefore recommend standardized fatigue assessment, with a validated instrument, in the work-up of sarcoidosis patients.

Physical training may be an important non-pharmacological intervention to reduce sarcoidosis-associated fatigue. Symptomatic sarcoidosis patients with fatigue and/or exercise limitation suffering from various manifestations might benefit from a supervised physical training program.

Evaluation of exercise capacity as well as muscle strength assessment should be considered in the evaluation of the severity and extent of the disease in symptomatic sarcoidosis patients with fatigue and/or exercise limitation.

Key issues

- The management of symptomatic sarcoidosis patients should focus not only pharmacological treatment strategies, but should combine all relevant aspects of a healthy life style to promote physical fitness.
- A better understanding of the principles of exercise training and the pathophysiology of sarcoidosis is essential for effective exercise program delivery.
- Despite the complexity of the signs and symptoms presented in sarcoidosis, supervised exercise training is a feasible and effective treatment for clinical improvement.
- Emerging research findings show significant enhancements of exercise capacity, fatigue and QoL among sarcoidosis patients after exercise training interventions.

Suggestions for future research

The multifactorial nature of sarcoidosis-related fatigue warrants further research to identify the different phenotypes of sarcoidosis-associated fatigue. The phenomenon of fatigue must be clarified in order to enhance medical as well as psychological and allied health care strategies to reduce fatigue.

Future research should focus on the effectiveness of physical training in symptomatic sarcoidosis patients, i.e. patients who have limited exercise capacity and decreased muscle strength and suffer from fatigue. The studies presented in this thesis showed short-term benefits of physical training in sarcoidosis, independent of age,

gender, time since diagnosis, and baseline pulmonary functions. Long-term benefits of this intervention should be investigated. Larger, randomized controlled studies are necessary to further build up the body of knowledge. It is also valuable to gather information to find out which patients will benefit most from this intervention. The assessment of factors that distinguish responders from non-responders is a challenging issue in sarcoidosis.

Muscle involvement and exercise limitations

Reduced muscle strength is a problem in a substantial number of sarcoidosis patients, regardless of their phenotype and clinical presentation. Therefore, the phenomenon of muscle dysfunction in sarcoidosis demands a wider appreciation and deeper understanding. The pathogenesis, molecular basis, and extent of muscle dysfunction should be further explored. Larger, robustly designed studies can help establish whether any muscle defects found represent consequences of systemic abnormalities stemming from the primary pathobiology and multisystemic character of sarcoidosis, or constitute manifestations of a primary myopathic process. The role of inflammation, oxidative stress, and physical inactivity, and the possible effect of sarcoidosis-specific therapy, should be better characterized. Finally, studies exploring the influence of sarcoidosis-specific treatment on aspects of skeletal muscle function, morphology, and enzyme activities should provide the required insights.

Lifestyle, food, and nutrition

Little research to date has focused on the relationship between diet, nutrition, and sarcoidosis. Functional foods and/or supplements may be used in the context of a healthy lifestyle. Inflammation is considered to be one of the major causes of the initiation of various chronic diseases such as asthma, cancer, cardiovascular disease, diabetes, obesity, inflammatory bowel disease, and osteoporosis, as well as neurological diseases like Parkinson's disease. Increasing evidence suggests that inflammatory markers, such as TNF-α, are the major factors regulating these inflammatory diseases. In addition to the benefits of pharmacological treatment and physical training, food may also play a role in the management of sarcoidosis, as food-derived anti-oxidants may provide subtle, but substantial effects reducing oxidative stress and inflammation. Anti-oxidant capacities of food and food-derived components (e.g. quercetin) have health promoting benefits and may prove a valuable addition. Future studies should investigate the benefit of combining all relevant aspects of a healthy life style in order to promote physical fitness.

Diagnostic work-up

Standardized assessment of non-specific symptoms (e.g. fatigue, SFN, exercise intolerance, muscle weakness, general weakness) is important. Since no standardized

assessment battery is as yet available, future studies should focus on the standardization and optimization of this assessment in sarcoidosis. Ultimately, it is of great interest to assess not only fatigue, but also the activity levels in daily life of patients with sarcoidosis. In the evaluation of treatment effect in general, it is important to compare activity levels at baseline and at follow-up. Patients who have attended a physical training program may experience persistent fatigue complaints even though their activity level has improved significantly. It is also interesting to investigate the relationship between fatigue and activity levels. More detailed information on patients' activity levels may facilitate tailoring the physical training program and providing advice regarding increased physical activity. Some patients may need a closely supervised physical training program, while for others, tailored advice and coaching 'at a distance' (e.g. by email or telephone) may be sufficient for them to exercise independently. A few studies have shown that e-health coaching is effective in patients with chronic illnesses, including COPD and diabetes mellitus, in terms of promoting health status and physical activity.[49-51] Evidence for the effectiveness of e-health in the management of sarcoidosis is lacking, so prospective randomized controlled trials are necessary to examine this.

Physical training in sarcoidosis: who, when, how, and how long?

Implementing physical training in the standard of care for sarcoidosis urgently requires guidelines. The heterogeneity of patients with sarcoidosis, representing different phenotypes which may or may not include lung parenchymal involvement, pain, fatigue, and/or muscle impairment, may require modification and program adjustment of the standard physical training format. The research described in this thesis constitutes a first step towards establishing guidelines by expanding the body of knowledge on the effectiveness of physical training and establishing recommendations regarding physical training in sarcoidosis. It remains unknown, however, which training parameters are to be used in sarcoidosis. Which patients will or will not respond to the intervention? What modalities are most effective in improving physical impairments and reducing sarcoidosis-related fatigue? Nor do we know the optimal frequency, intensity, and duration of the training program. These matters should be addressed in future research, in order to optimize treatment strategies.

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