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ORIGINAL PAPER

Combining thrombopoietin receptor agonists with immunosuppressive drugs in adult patients with multirefractory immune thrombocytopenia, an update on the French experience

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Summary
Combining drugs could be an effective option for treating multirefractory ITP, that is, patients not responding to rituximab, thrombopoietin receptor agonists (TPO-RA) and splenectomy. We conducted a retrospective, multicenter, observational study including multirefractory ITP patients who received a combination of a TPO-RA and an immunosuppressive drug. We included 39 patients (67% women, median age 59 years [range 21–96]), with a median ITP duration of 57 months [3–393] and a median platelet count at initiation of 10×10^9/L [1–35]. The combination regimen was given for a median duration of 12 months [1–103] and included eltrombopag (51%) or romiplostim (49%), associated with mycophenolate mofetil (54%), azathioprine (36%), cyclophosphamide (5%), cyclosporin (3%) or everolimus (3%). Overall, 30 patients (77%) achieved at least a response (platelet count $\geq 30 \times 10^9$/L and at least doubling baseline during at least 3 months), including 24 complete responses (platelet count $>100 \times 10^9$/L during at least 3 months) with a median time to response of 30 days [7–270] and a median duration of response of 15 months [4–63]. Severe adverse event related to ITP treatment was observed in 31%. In conclusion, this study confirms that some patients with multirefractory ITP can achieve long lasting response with this combination.

KEYWORDS
combination therapy, immunosuppressive drug, ITP, TPO-RA

INTRODUCTION

Despite increasing therapeutic options for the management of immune thrombocytopenia (ITP), some patients remain difficult to treat with impaired quality of life and an increased risk of mortality.[1,2] Primary treatment options for chronic ITP include rituximab, thrombopoietin receptor agonists (TPO-RAs) and splenectomy.[3] When all these options have failed (or in case of contra-indication), ITP can be considered as being multirefractory, and alternative treatments are needed.[1] Conventional immunosuppressive drugs have been used for decades in ITP with highly variable response rates described mainly on small, retrospective studies, but with a well-known safety profile due to their widespread use in autoimmunity and transplantation settings. Among them, azathioprine (AZA) is considered safe during pregnancy,[3] and resulted in a response rate of 66% in a systematic review[4] and 38.1% at day 90 in a recent retrospective study of 63 patients.[5] Mycophenolate mofetil (MMF), another purine inhibitor, is increasingly used over AZA, with overall response rates of 40%–60% in retrospective studies[6–8] and have also been investigated more recently throughout a prospective randomized study as a first line treatment.[9] Other immunosuppressive drugs such as cyclosporin A (CSA),[10–12] cyclophosphamide[13,14] or rapamycin have also been used with variable efficacy rates for patients with ITP.[15–18] Combining immunosuppressive drugs with other medications has been proposed as a rescue strategy in patients with refractory ITP.[19–22] Based on a previous retrospective cohort upon 37 multirefractory ITP patients reported by our group, only 1 out of 14 patients who received an immunosuppressive drug as a single agent eventually achieved a response, while 7 out of 10 patients treated with a combination therapy including a TPO-RA and an immunosuppressive drug achieved a response, suggesting a synergistic effect.[1] Since then, this strategy has been used for managing adult patients with severe multirefractory ITP by most of the centers from the network of the French reference center for adult immune cytopenias.

Here, we report the data of a multicenter retrospective analysis upon 39 multirefractory patients with ITP treated by such combination and their outcomes.

PATIENTS AND METHODS

We conducted a retrospective, multicenter, observational study in 17 centers in France. Inclusion criteria were: (1) patients with chronic (>12 months) or persistent (>3 months) ITP according to international guidelines;[3] (2) patients who failed to respond to their last course of rituximab, to both TPO-RAs that are available in France (i.e. romiplostim and eltrombopag) given at the maximum dose (although patients could have an initial transient response), and to splenectomy (except if splenectomy was contra-indicated or refused by the patient), thereafter referred to as multirefractory ITP; and (3) patients who received a combination of one TPO-RA (romiplostim or eltrombopag) and an immunosuppressor (mycophenolate mofetil, azathioprine, cyclosporin, everolimus, or cyclophosphamide), thereafter referred to as combination therapy between 2009 and 2021. Because fostamatinib became available in France only in October 2021, no patients from this study received this treatment with the combination therapy. Combination drugs were selected by the treating physician based on local practice. We excluded patients who received an immunosuppressor for another reason than ITP. Patients were identified in France throughout the network of the national reference centre for adult' autoimmune

cytopenia (CERECAI). Clinical and biological data were retrospectively collected using a standardized form. Response (R) was defined as platelet count $\geq 30 \times 10^9$/L and at least doubling baseline without complete response, and complete response (CR) was defined as platelet count $>100 \times 10^9$/L. As some patients received a short course of corticosteroids or had platelet count fluctuation, we chose to consider only R and CR lasting at least 3 consecutive months. Patients with no responses or responses lasting less than 3 months were considered as having treatment failure. Adverse events were recorded during follow-up, and serious adverse events were defined according to the European Medicines Agency.[23] Fisher's exact test was used to compare proportions as appropriate. A p-value ≤0.05 was considered statistically significant. Statistical analyses involved use of GraphPad Prism 4.0. This study was conducted in compliance with the Declaration of Helsinki principles and was approved by the Institutional Review Boards Comité de Protection des Personnes (CPP) Ile-de-France IX.

RESULTS

Characteristics of patients

Thirty-nine patients with multirefractory ITP (67% women, median age 59 years [range 21–96] at combination therapy initiation) were included (Table 1). Eleven of them were previously included in our previous study published 6 years ago (1). Eight of them had secondary ITP, including 2 Evans syndromes, 2 systemic lupus (including 1 with secondary antiphospholipid syndrome [APS]), 1 primary APS, 1 Sjögren syndrome, 1 marginal zone lymphoma (untreated) and 1 Waldenstrom's macroglobulinaemia (treated by rituximab and cyclophosphamide 4 years before combination). Seven patients (18%) had a monoclonal gammopathy of undetermined significance, and 15 (38%) had positive antinuclear antibodies (titre ≥1/160). A bone marrow examination was performed in all patients with findings consistent with ITP, except in four patients that otherwise responded to corticosteroids. All patients had previously received corticosteroids, and 49% were corticosteroid-resistant and 92% had previously received intravenous immunoglobulin (with no response in 17%). Seven patients (18%) had a previous transient response to rituximab but all patients failed to achieve a response to their last course, and 49% had already received one or more immunosuppressor without TPO-RA, none of whom achieved a response. Although all patients failed to respond to eltrombopag and romiplostim monotherapy, 15 of them initially achieved at least a R after TPO-RA (including 6 initial R, and 9 initial CR) but subsequently failed to respond despite maximum approved dose increase and TPO-RA switch. Twenty-nine patients (74%) had undergone splenectomy, whereas splenectomy was contra-indicated in the remaining 10 patients for the following reasons: age and comorbidities ($n=5$), APS ($n=2$), underlying cirrhosis ($N=2$) and patient refusal ($n=1$). At time of initiation of the combination therapy, median ITP duration was 57 months [range 3–393], with 90% of chronic and 10% of persistent ITP (Table 1). The median platelet count at the time of inclusion was 10×10^9/L [range 1–35] and 64% of patients had bleeding symptoms.

Combination therapy included eltrombopag ($n=20$) or romiplostim ($n=19$) (at the maximal approved dose in 85%), associated with either mycophenolate mofetil ($n=21$), azathioprine ($n=14$), cyclophosphamide ($n=2$), cyclosporin ($n=1$) or everolimus ($n=1$), for a median duration of 12 months [range 1–103]. For 30 patients (85%), the time between the initiation of the TPO-RA and the immunosuppressor was less than 3 months, while in 8 patients (21%) TPO-RA was given more than 3 months with no response as a single treatment before the introduction of an immunosuppressor. In addition to the combination therapy, 17 patients (43%) were

TABLE 1 Patients characteristics.

	All patients ($n=39$)
Women	26 (67)
Age (years, median, range)	59 [21–96]
ITP duration (months), median (range)	57 [3–393]
Chronic	35 (90)
Persistent	4 (10)
Bleeding symptoms at inclusion	25 (64)
Median platelet count at inclusion ($\times 10^9$/L, range)	10 [1–35]
M protein	9 (23)
Antinuclear antibody (titre ≥1/160)	15 (38)
Secondary ITP	8 (21)
Number of different treatment-lines (median, range)	5 [5–11]
Treatments received before combination therapy	
Corticosteroids	39 (100)
Corticosteroids refractoriness	19 (49)
Intravenous immunoglobulin	36 (92)
Rituximab	39 (100)
Splenectomy	29 (74)
Dapsone	23 (59)
Hydroxychloroquine	11 (28)
Immunosuppressor	19 (49)
Combination therapy	
TPO-RA	
Eltrombopag	20 (51)
Romiplostim	19 (49)
Immunosuppressor	
Mycophenolate mofetil	21 (54)
Azathioprine	14 (36)
Cyclophosphamide	2 (5)
Cyclosporin	1 (3)
Everolimus	1 (3)

Note: Unless indicated, numbers are patients (percentages).

TABLE 2 Patients outcomes according the type of combination therapy.

	All patients ($N=39$)	Previous immunosuppressive drug use ($N=19$)	No treatment modification in the 3 months before combination ($N=25$)	No corticosteroids ($N=22$)	MMF ($N=21$)	AZA ($N=14$)	Eltrombopag ($N=20$)	Romiplostim ($N=19$)
Overall response	30 (77)	17 (89)	18 (72)	15 (68)	17 (81)	9 (64)	17 (85)	13 (68)
Complete response	24 (62)	13 (68)	14 (56)	13 (59)	16 (76)	5 (36)	13 (65)	11 (58)
Response	6 (15)	4 (21)	4 (16)	2 (9)	1 (5)	4 (29)	4 (20)	2 (11)
Relapse after response	10 (33)	7 (41)	6 (33)	5 (33)	4 (24)	4 (44)	7 (41)	3 (23)
Treatment failure	9 (23)	2 (11)	7 (28)	7 (32)	4 (19)	5 (36)	3 (15)	6 (32)

Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil.

also given corticosteroids: 7 patients had a short course of high dose corticosteroids, and 10 were treated with a low dose of prednisone (i.e. ≤10 mg/day) on a long-term. Seven patients (18%) also received hydroxychloroquine with the combination. Twenty-five patients (64%) had no treatment modification in the 3 months preceding the introduction of the combination therapy. Splenectomy was performed in 2 patients (failure) within the month preceding the initiation of combination therapy, and 1 patient who was previously treated with bortezomib for refractory ITP received the last cycle without response 3 months before the combination therapy was started. No patient received repeated infusions of intravenous immunoglobulin.

Efficacy

Overall 30 patients (77%) achieved at least a response, including 6 R and 24 CR (Table 2; Figure 1). Among responders, the median time to response was 30 days [range 7–270], and the median duration of the response was 15 months [range 4–63].

We found no significant difference in overall response rates (ORR) in the subgroups of patients who did not receive corticosteroids (ORR 68%), and in patients who had no treatment modification in the 3 months before combination therapy was initiated (ORR 72%) (Table 2 and Figure S1). ORR was 89% in the 19 patients that previously received an immunosuppressive drug (and failed to respond). Among them, 7 patients received the same drug in the combination, and all of the patients responded to it (5 CR, 2 R). We did not find significant differences between patients treated by eltrombopag or romiplostim, or between patients treated by MMF and AZA (Table 2; Figure S1).

Long term outcome

After a median follow up of 21 months [range 5–103] after the initiation of combination therapy, 19 patients among the 30 responders maintained a response (63%) and 11 (37%) relapsed (Table 2; Figure 2). The median duration of the response was 15 months [range 4–63]. Overall, 19 patients eventually stopped the combination therapy because of failure/relapse ($n=11$), complete response ($n=5$), adverse event ($n=1$), pregnancy ($n=1$) and Waldenstrom's macroglobulinaemia progression ($n=1$). Among the 5 patients that stopped the combination because of CR, 1 stopped the TPO-RA (no relapse), 2 stopped the immunosuppressive agent (no relapse), and 2 stopped both, including 1 patient that relapsed after 51 months then responded again after restarting combination. Among the 17 patients that were on corticosteroids at combination initiation, 9 (53%) eventually discontinued corticosteroids during follow-up. Bleeding symptoms were observed in 7 patients during follow-up (patients with failure, $N=4$ and relapsing patients with initial R or CR, $N=3$).

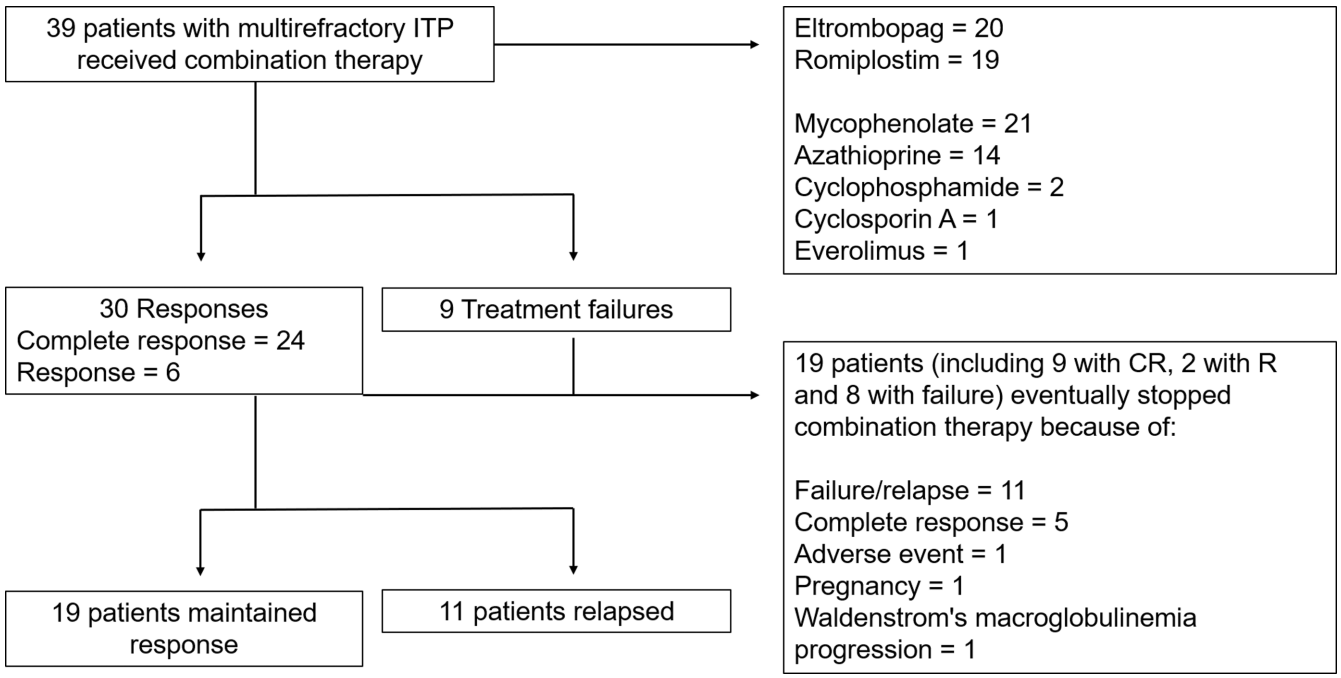

FIGURE 1 Patients flow chart.

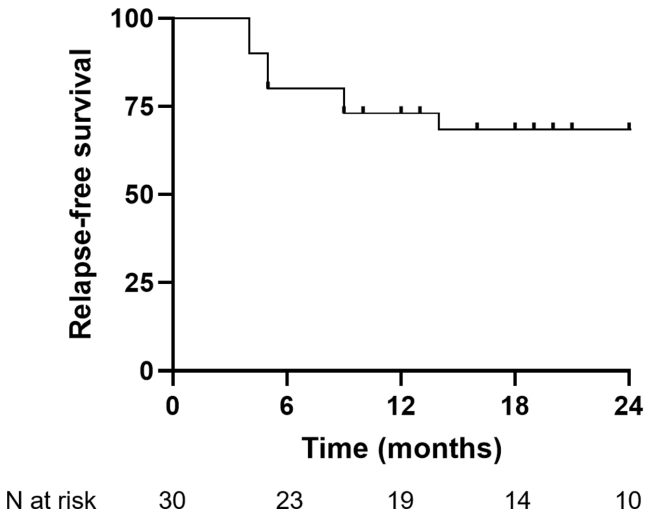

FIGURE 2 Kaplan–Meier curve for relapse-free survival of patients responding to combination therapy. Month 0 is the time of first response after combination therapy. Events are defined by relapse or death. Patients are censored if no event was observed at last follow-up. Number at risk are indicated below the curve.

Adverse events

During the follow-up, 17 (44%) patients had at least one adverse event imputable to treatment and 12 (31%) had at least one severe adverse event (Table 3). Severe adverse events included a thromboembolic event in 5 patients. One patient had known APS and had central retinal artery occlusion. The remaining 4 patients were splenectomized without APS and had deep vein thrombosis and pulmonary embolism ($n = 3$) associated with carotid thrombosis in one of them, and cerebral venous thrombosis ($n = 1$). Four patients had an infectious event while taking the combination, including 2 requiring hospitalization (1 cholecystitis and 1 bacterial sepsis in a cirrhotic patient) without admission in intensive care unit. One patient died of pancreatic adenocarcinoma (age 83 years). Among the 21 patients receiving MMF, 6 (29%)

TABLE 3 Adverse events.

	All patients ($N = 39$)
At least one adverse event imputable to treatment	17 (44)
At least one severe adverse event	12 (31)
Death[a]	1 (3)
Gastro-intestinal manifestations (MMF)	6 (15)
Thrombosis[b]	5 (13)
Infection[c]	5 (13)
Cancer[d]	2 (5)
Pancytopenia (AZA)	1 (3)
Elevated liver enzymes (eltrombopag)	1 (3)
Arterial hypertension (CSA)	1 (3)

Abbreviations: AZA, azathioprine; CSA, cyclosporin; MMF, mycophenolate mofetil.

[a]Pancreatic adenocarcinoma (age 83 years).

[b]4 patients without antiphospholipid syndrome, including 2 patients with deep vein thrombosis and pulmonary embolism, 1 patient with deep vein thrombosis, pulmonary embolism and carotid thrombosis, 1 patient with cerebral venous thrombosis, and 1 patient with antiphospholipid syndrome and central retinal artery occlusion.

[c]2 herpes zoster, 1 cholecystitis, 1 dental abscess, 1 bacterial sepsis (cirrhotic patient).

[d]1 Pancreatic adenocarcinoma and 1 basocellular carcinoma.

had mild gastro-intestinal symptoms (abdominal pain and/or diarrhoea) requiring a switch to mycophenolic acid in 2 and dose-adjustment in 1.

DISCUSSION

In this multicenter observational study on 39 patients with multirefractory ITP, combination therapy including a TPO-RA and an immunosuppressive drug resulted in high response rate and some durable responses. It must be emphasized that TPO-RA monotherapy was previously ineffective in all patients, and that 49% had previously received an immunosuppressive drug with no platelet response. Among those, 7 patients were rechallenged with the same immunosuppressive drug and all responded in combination with a TPO-RA. These results suggest that immunosuppressant therapy may restore the efficacy of TPO-RAs by dampening the pathogenic autoimmune process in a significant proportion of patients. This synergistic effect confirms the previous signal of efficacy of such a combination strategy for managing multirefractory patients previously reported by our group.[1]

We confirm in this cohort the high morbidity associated with multirefractory ITP, characterized by a high rate of infections and thrombosis. The risk of venous and arterial thrombotic events in patients receiving TPO-RAs has already been reported, and most patients had additional thrombotic risk factors such as comorbidities, previous splenectomy, hospitalization, and/or, to a lesser extent, ongoing corticosteroid therapy. Infectious events were mainly non-severe, and importantly no patient was admitted in intensive care unit, although the infectious risk can be high in multirefractory[1] and splenectomized[24] patients. The risk benefit balance therefore appears clearly in favour of combination therapy in multirefractory patients. Although the exact prevalence of multirefractory ITP is unknown, preliminary data from a prospective French registry estimated that 2.2% of adult ITP patients needed ITP treatment after exposure to eltrombopag, romiplostim and rituximab.[25]

Other options have been proposed for multirefractory patients. Combining intravenous immunoglobulin to inhibit platelet destruction, with an association of TPO-RA to increase platelet production and an immunosuppressant (either cyclosporine or MMF) to inhibit T cell effects, has been reported as effective.[21] However, this strategy has not been adopted by our group because there is a tight supply of intravenous immunoglobulin in Europe and this treatment requires iterative admissions in hospital which is a burden for the patient. This may be an attractive strategy for patients who do not respond to the combination of TPO-RA and immunosuppressant. We also did not attempt to switch TPO-RA if the combination with an immunosuppressant failed, or to switch to avatrombopag[26] as it is not available in our country. In the near future, other treatment options may be considered, in particular emerging therapies such as fostamatinib, FcRn inhibitors or BTK inhibitors that may have a place in combination regimens for the most severe patients. Whether combining these new therapeutic options with other ITP standard therapies is safe and effective remains to be evaluated, as well as the use of combination therapy earlier in the course of the disease in non-refractory patients.

It is difficult to conclude on which combination should be used given the limited number of patients and the retrospective design. Response rates were similar between both TPO-RAs used in this study. Although not significant, mycophenolate mofetil had slightly better response rates over azathioprine (81% vs. 64%), and has also been tested in a randomized trial.[9]

This retrospective and uncontrolled study has obviously some limitations, and results should be interpreted with caution. Patients were heterogeneous with several TPO-RAs and immunosuppressive drugs used in combination, and the number of patients was too limited to correctly analyse these differences. Nevertheless, given the rarity of multirefractory ITP, it is unlikely that a randomized clinical trial will ever be conducted in this patient population. Corticosteroids which were given to 44% of patients along with the combination therapy could have transiently increased the initial response rate, but to avoid such bias, we only considered responses lasting at least 3 months. It is also possible that some patients respond to the immunosuppressive drug, with minor benefit of the associated TPO-RA. However, the fact that response rates were not different between patients previously exposed to an immunosuppressive drug without success and those with first prescription argues against this hypothesis, as well as the responses observed in patients rechallenged with the same immunosuppressive drug. Similarly, response rates were not different between patients receiving or not corticosteroids.

In summary, these data confirm that some adult patients with multirefractory ITP can achieve long lasting responses with a combination of a TPO-RA and an immunosuppressive drug, with an acceptable safety profile for this population.

AUTHOR CONTRIBUTIONS

Etienne Crickx, Matthieu Mahévas, Marc Michel and Bertrand Godeau designed the study and analysed the data. Etienne Crickx, Mikael Ebbo, Etienne Rivière, Odile Souchaud-Debouverie, Louis Terriou, Sylvain Audia, Marc Ruivard, Bouchra Asli, Jean-Pierre Marolleau, Nadine Méaux-Ruault, Mathieu Gerfaud-Valentin, Philippe Audeguy, Mohamed Hamidou, Mohamed Hamidou, Selim Corm, Xavier Delbrel, Jean Fontan, Delphine Lebon, Christelle Mausservey, Guillaume Moulis and Nicolas Limal contributed to data acquisition. All authors revised the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

MMa received funds for research from GSK and fees from Amgen and Novartis for lectures. BG served as an expert for Amgen, Novartis, Grifols and Sobi; MMi received honoraria (advisory boards, speaker fees) from Novartis, Amgen, UCB,

Argenx, Alexion and Sanofi. EC received honoraria (advisory boards, speaker fees) from Novartis, UCB and Sanofi. LT received honoraria and/or research or educational support from Novartis, AstraZeneca, Grifols and Amgen. MGV received honoraria (advisory boards, speaker fees) from Amgen and Novartis (advisory boards, speaker fees).

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

This study was conducted in compliance with the Declaration of Helsinki principles and was approved by the Institutional Review Boards Comité de Protection des Personnes (CPP) Ile-de-France IX.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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