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A critical assessment of treatment options for idiopathic pulmonary fibrosis

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Abstract

Background—To date, no management approach has proven to be efficacious for the treatment of idiopathic pulmonary fibrosis (IPF). Consequently, therapeutic options remain controversial and confusing for many clinicians. We sought to formally review available evidence on treatment options for IPF and to have a diverse panel of physicians rate the “appropriateness,” “inappropriateness,” or “uncertainty” of some of the available therapeutic options.

Methods—The RAND/UCLA Appropriateness Method was used to review and rate multiple clinical scenarios for the treatment of IPF. The panel was composed of nine physicians from geographically diverse areas who received a systematic review on the risks and benefits of commonly used treatments for IPF as background.

Results—A total of 324 clinical scenarios were rated: 25% as appropriate; 39%, uncertain; and 36%, inappropriate. The panel disagreed about 12% of the therapy indications in the final ratings, falling from 26% in the first-round ratings.

Conclusions—Key themes emerged from the consensus process. Lacking evidence for a definitive therapy, it was considered most appropriate to enroll eligible patients in clinical trials and refer eligible patients for transplant evaluation. For patients without access to clinical trials, the committee was not unanimous regarding treatment recommendations. It was considered inappropriate for patients with a confident diagnosis of IPF to be treated with corticosteroids as the sole agent: corticosteroids should be used in conjunction with azathioprine. With progressive disease despite

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such combination use, there was agreement for the use of interferon gamma-1b in patients unwilling or unable to participate in available clinical trials.

Keywords

Pulmonary fibrosis; Fibrosing alveolitis; Interstitial pneumonia; Therapeutics; Human; Adult

Abbreviations

IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; HRCT: high resolution computed tomography scan; IFN: interferon gamma-1b; FVC: forced vital capacity

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease that causes significant morbidity and mortality. Patients' short survival time, high mortality, and generally rapid decline raise the importance of initiating optimal therapy early [1]. In 2000, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) adopted a uniform classification for idiopathic pulmonary fibrosis [2]. This classification has greatly facilitated research on diagnosis and management of IPF. In addition, advances in our understanding of the mechanisms of injury and repair in lung fibrosis has lead to the development of several novel agents, whose therapeutic benefits remain unconfirmed.

The ATS/ERS guidelines outlined a management approach for IPF [2]. To date, however, no management approach has proven to be efficacious for the treatment of IPF. Consequently, therapeutic options remain controversial and confusing for many clinicians. When definitive evidence is lacking, the RAND/UCLA consensus panel method has been shown to provide the most up-to-date guidance, combining an evidence-based review with the practical experience of clinician-leaders in the field. This method has been used for diverse topics, including treatment of depression in women, sentinel lymph node biopsy in melanoma, use of NSAIDs/Cox-2 inhibitors with proton-pump inhibitors, and appropriateness of surgery for sciatica [3–6]. It is with this background that we report the opinions of a group of highly selected IPF experts. All had reviewed an evidence-based summary of the literature, and several of the panelists had conducted the primary studies themselves. The purpose of this critical assessment is to identify appropriate therapeutic options for patients presenting with various levels of objective and subjective impairment, but with a confident diagnosis of IPF.

Methods and Materials

To develop appropriateness measures for IPF treatment options, we used the extensively validated RAND/UCLA Appropriateness Method to determine the evidence for and against various interventions [7]. A geographically diverse expert panel received a systematic review of the literature prepared by one of us (NS) which described the benefits and risks of these interventions [8]. A copy of this systematic review is available from Dr. Shah upon request. Studies and review articles about the treatment of IPF were identified in Medline (1966-September 2003) and the Cochrane Library (Issue 3, 2003). To be included in this systematic review, studies had to be conducted in adult men or women with the title available in English. The Medline search used the following strategy:

((cryptogenic fibrosing alveolitis) OR (idiopathic pulmonary fibrosis) OR (usual interstitial pneumonia)) AND (randomized controlled trial [PTYP] OR case-control studies

[MH:NOEXP] OR cohort studies [MH:NOEXP] OR drug therapy [SH] OR therapeutic use [SH:NOEXP] OR random* [WORD])

Studies selected for analysis met the following requirements: (1) the study was observational or interventional with a comparison group (e.g., case-control, cohort, quasi-experimental, or experimental); (2) there was longitudinal ascertainment of exposure and disease (ascertainment could be prospective or historical, but not cross-sectional); (3) the study reported data on differential outcomes in at least two groups, or the study included a summary estimate (odds ratio or relative risk) with reported confidence intervals or a precise p-value; (4) the criteria used for identifying IPF had to be defined in the study. In addition to the peer-reviewed literature identified above, we sought out available data for drugs that have been phase 3 tested (including abstracts, case reports, and unpublished manufacturers data). Phase 1 or 2 data were excluded. We recognize that material in abstracts is not peer reviewed and is not the norm for literature reviews of this type. For citations with no available abstract, the full text was retrieved. References from editorials, letters, and reviews were used to identify additional citations potentially not indexed by Medline. For datasets that were presented in multiple publications, the most up-to-date results with the longest follow-up or most pertinent outcomes reported were selected for analysis.

Clinical scenarios

We attempted to create a comprehensive list of common scenarios that might arise in clinical practice. Patients were categorized according to hypothetical situations or clinical scenarios based on combinations of various clinical factors. The complete list of descriptors is given in Table I. These include patient age and comorbidities, evidence of objective impairment, and prior therapies attempted. These clinical scenarios were then rated for each of the considered treatment options.

Consensus panel

We convened a panel of nine physicians representing a diversity of practice settings (6 universities and 3 communities) and geographic sites. A pool of potential panelists was identified from a combination of authors of key clinical trials, and recognized community-based practitioners. The final selection, made in consultation with a leader in the field (PN), balanced practice setting and geographic factors. The list of consensus panel members and their affiliations is given in the acknowledgements.

The panelists were sent summaries of the systematic review and a list of the references that met the criteria noted above. Each panelist was asked to rate treatment options for the series of clinical scenarios. Each indication was rated on a 9-point scale of appropriateness (9 indicated extremely appropriate; 5, uncertain; and 1, extremely inappropriate).

At a subsequent 2-day meeting, the panelists discussed the findings from the literature review and clarified any issues about treatment approaches or provided input regarding additional studies currently under investigation. They reviewed the summarized first-round ratings, revised the indications structure, modified the definitions of key terms, and discussed reasons for the degree of agreement or disagreement in ratings from the first round. The panel then independently and confidentially re-rated the revised clinical scenarios.

Appropriateness was defined as the expected health benefits of the treatment option or therapy exceeding its expected negative health consequences by a sufficiently wide margin to justify it. The final rating was the median score of the nine panelists. We considered that indications were appropriate for median ratings between 7 and 9 (without disagreement), inappropriate for median ratings between 1 and 3 (without disagreement), and uncertain for median ratings

between 4 and 6 or if panelists disagreed. The consensus method did not force agreement. We defined disagreement as occurring when at least 2 panelists rated the indication appropriate and at least 2 rated the indication inappropriate regardless of the median rating. Data are reported as Appropriate, Inappropriate, or Uncertain.

Results

The rating structure and clinical scenarios resulted in 324 permutations. As shown in Table II, despite the complexity of the rating structure, the final ratings (available upon request) were readily grouped for simpler presentation. We collapsed the separate indications in which the categorization of appropriateness did not differ based on clinical factors (e.g., all were appropriate, uncertain, or inappropriate). Consistent with generally accepted practice in applying the RAND/UCLA consensus methods, we did not perform statistical testing because of the descriptive nature of this analysis and the small sample size (see Table II). Cells shaded in pink were rated inappropriate, in green as appropriate, in white as uncertain, and in yellow when panelist disagreement occurred.

Of the indications for IPF therapy, 25% were rated as appropriate; 39%, uncertain; and 36%, inappropriate. According to our definition, the panel disagreed about 12% of the therapy indications in the final ratings, falling from 26% in the first-round ratings. In Table II, each column pertains to one therapeutic option and there are 24 different clinical scenarios where the therapy might be considered. Another measure of consensus considers how often the panel disagreed on the use of a particular therapy. This type of disagreement was "Intermediate" (defined as 4 or fewer scenarios with disagreement among the 24 clinical scenarios in the same column in Table II) or "Moderate" (defined as greater than 4 scenarios with disagreement in a given column).

Areas of panel unanimity

For some therapeutic interventions, the panel had a high degree of consensus. For example, the panel concluded that *corticosteroids alone* are always "inappropriate" regardless of clinical scenario. *Cyclophosphamide plus steroids* are "inappropriate" for those aged 65–79 and "uncertain" as initial therapy for those under 65. Referring patients for *enrollment in randomized trials* is "appropriate" under all scenarios. Referring patients for *transplant evaluation* is "appropriate" for patients under 65 and "inappropriate" for those aged over 65. The appropriateness of using *pirfenidone* is "uncertain" under all scenarios (see Table III).

Areas with intermediate disagreement

The panel rated some therapies with less consensus. The panel considered *Azathioprine plus steroids* appropriate as initial therapy in those under 65 (unless they showed signs of severe objective impairment when it was "uncertain"), and were "uncertain" about its use as initial therapy in those aged 65–79. The panel had disagreement regarding the role of azathioprine plus steroids in patients who had tried and failed on steroids alone. The panel rated *Interferon gamma* as "appropriate" for patients who have failed initial therapy with either steroids or cytotoxic agents and have mild to moderate objective impairment, "uncertain" as initial therapy, and "inappropriate" as initial therapy in patients with severe objective impairment. The panel disagreed on its use in patients < 65 with severe objective impairment who had failed prior therapies. *Interferon gamma plus steroids* were rated "appropriate" as initial therapy for those under 65 with mild or moderate disease who have failed prior cytotoxic agents (with or without corticosteroid exposure). Disagreement was most pronounced regarding its role as initial therapy.

Areas with moderate disagreement

The panel had disagreement about when no therapy should be considered. Consensus was achieved that providing *no therapy* is "inappropriate" for those under 65 who have not received other therapy. The remaining scenarios had significant areas of disagreement.

Discussion

In conducting this evidence-based review, the panel's goal was to provide practical guidance to busy clinicians, using the RAND/UCLA Appropriateness Method to help synthesize evidence and experience. We found that the evidence base for much IPF treatment is suboptimal, with the clearest evidence suggesting 1) the need for additional randomized trials, 2) early referral of eligible patients for lung transplant evaluation, and 3) no role for corticosteroids alone in cases of confirmed IPF.

The utility of the RAND/UCLA method is most easily identifiable in areas where the definitive randomized, double-blind clinical trial has not been conducted, but the overall weight of the evidence is compelling. For example, no randomized trial has ever been conducted comparing corticosteroids alone to placebo in patients with confirmed IPF (defined using recent criteria). However, the data that are available show no objective clinical benefit (and only transient subjective benefit) from the use of corticosteroids in clearly-defined IPF [9–11]. Hence in reviewing the body of evidence, the panel had consensus in concluding that for cases of confirmed IPF, corticosteroids alone have no role as the sole, initial therapy. Three other important themes emerged without disagreement.

First, if a prospective clinical trial is available, referral for participation was always considered appropriate. Until there is a definitive treatment for IPF, a randomized trial may be one of the best ways for a patient to receive potentially beneficial treatments, while advancing the state of the science for future patients with IPF.

Second, the appropriateness of referral for allogenic lung transplantation depended upon the patient's age: inappropriate in those aged 65 or older, and appropriate for younger individuals. Lung transplant is not currently an option for most patients over 65 in the United States, though some centers will consider individual patients on a case-by-case basis.

Third, although preliminary data appear promising, the panel rated the use of pirfenidone as "uncertain" [12,13]. This drug is not currently routinely available to US physicians, and at this time it is not possible to make a recommendation regarding the appropriateness for clinical practice. At the time of the literature review data were also lacking for other agents being investigated for efficacy in IPF, including bosentan, thalidomide, etanercept, and imatinib.

Two themes emerged with intermediate levels of disagreement: for the use of azathioprine and corticosteroids, and interferon gamma-1b.

Initiating therapy with a trial of azathioprine and corticosteroids was rated appropriate by the panel for patients under age 65, with mild-to-moderate impairment, who had never been treated or had failed steroid therapy alone. Prospective clinical trial data comparing azathioprine to placebo were not available. One randomized trial comparing azathioprine and corticosteroids to corticosteroids alone in 27 newly-diagnosed patients with IPF found no significant differences in the primary analyses for lung function, oxygenation, or survival. The secondary analyses adjusted for age found a survival advantage for the group that received azathioprine [14]. The panelists favored azathioprine over cyclophosphamide because of the potential differences in side effects of the two drugs.

Use of interferon gamma-1b as first line therapy was deemed uncertain for those under 65 and inappropriate in patients over 65 with severe impairment. The panel rated the use of interferon gamma-1b as appropriate – not as first line therapy – but only after initial management had failed in patients with mild-to-moderate impairment (FVC > 55% and D_{LCO} > 35%). A recent, large randomized trial of interferon has failed to demonstrate significant efficacy compared to placebo [15]. Efficacy was based on the combined primary outcome of death or disease progression (defined as an FVC decrease of 10%, A-a gradient increase of 5mm Hg, or death) which was not significantly different for the group randomized to IFN-γ1b relative to placebo control (OR 0.80 (0.52, 1.24)). However, subgroup analyses, which are generally considered at best hypothesis generating, showed a possible survival benefit for patients with mild-to-moderate impairment at time of randomization.

The RAND/UCLA Appropriateness Method

The validity and usefulness of guidelines depend on the method used. We used the RAND/UCLA Appropriateness Method, a well-studied approach that blends evidence from the literature with an expert consensus process [7]. No panel can deduce the results of a definitive randomized controlled trial before it has been conducted. It can, however, assess what is known today in as formal and unbiased fashion as possible. The panel received an extensive systematic review of the literature (see Table IV for the studies reviewed in detail). The systematic review included data on the potential benefits and risks of treatment options for IPF. At the time of the panel review, results from the IFN gamma-1b randomized trial were available as the results and subgroup/exploratory analyses had been presented by some of the panel members at scientific meetings. Thus, the panel had an opportunity to consider these most recent data in detail.

Consistent with the RAND/UCLA Appropriateness Method, the panel had a diverse US composition. The panel included representatives from academic as well as community-based practice. The panelists represented all major geographic regions of the US, and clinical practice in the US tends to be similar to that in Europe for this disease. The panel reflected multiple viewpoints and this mitigates potential geographic and practice-type bias.

The development of the guidelines used a quantitative process. Each panelist rated 324 clinical scenarios on a 9-point risk-benefit scale from least appropriate (1) to most appropriate (9). These scenarios reflect real-world combinations of clinical factors. The final ratings were calculated as the median scores among the nine panelists, not necessarily reflecting each panelist's opinion. When statistical disagreement occurred (i.e., at least 2 panelists rated a scenario appropriate and at least 2 panelists rated that same scenario inappropriate), that scenario was given a rating of uncertain.

Conclusions

It is most appropriate to enroll eligible patients in clinical trials and refer eligible patients for transplant evaluation. The lack of conclusive evidence for an effective therapy at this time and the opportunity for patients to enroll in clinical trials mandates physicians to encourage this when available. For patients who do not have access to clinical trials, the committee was not in unanimous agreement regarding treatment recommendations. It was considered inappropriate for patients with a confident diagnosis of IPF to be treated with corticosteroids as the sole agent. Corticosteroids should be used in conjunction with azathioprine. With progressive disease despite treatment with corticosteroids and azathioprine, there was agreement for the use of interferon gamma-1b in patients unwilling or unable to participate in available clinical trials.

Acknowledgements

Consensus panel members included Robert M. Jackson (University of Alabama at Birmingham), Steven D. Nathan (Inova Fairfax Hospital), Maria Padilla (North Shore University Medical Center), Melissa Bruce Rhodes (Georgia Lung Associates), Gregory Tino (University of Pennsylvania), Marvin Schwarz (University of Colorado Health Sciences Center), Ganesh Raghu (University of Washington), Paul Noble (Yale University School of Medicine), and Talmadge E. King, Jr. (University of California, San Francisco).

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Appendix: Declaration of all potential conflicts of interest

Nirav R. Shah: None – Robert M. Jackson: Consultancies: InterMune, Genzyme Honoraria and Grants received: InterMune. Clinical investigator: InterMune, Actelion and Novartis studies of IPF therapies – Talmadge E. King, Jr.: Consultancies: Alexza, Actelion, AstraZeneca, Biogen, Centocor, FibroGen, Genzyme, Human Genome Sciences, InterMune, Merck, Nektar, Shionogi & Co., Wyeth-Ayerst – Ganesh Raghu: Consultancies/Honoraria: Actelion, Amgen, AstraZeneca, Aventis, Biogen, Centocor, FibroGen, Genzyme, InterMune, Shionogi & Co., Wyeth-Ayerst – Melissa Bruce Rhodes: Consultancies/Honoraria: InterMune – Marvin Schwarz: Honoraria: InterMune – Steve Nathan: Consultancies/Honoraria/Research Funding: InterMune – Paul Noble: Consultancies: InterMune, Genzyme, Mellenium: Steering Committee: GIPF-001 and GIPF-007. Honoraria: InterMune –Maria L. Padilla: Consultancies/Honoraria: InterMune – Greg Tino: Consultancies/Honoraria/Grant support: InterMune – Robert DuBois: None

Table I

Clinical indications and treatment options rated for IPF

Patient age and comorbidity

- Age less than 65 and not significantly compromised by comorbid conditions,
- Age greater than 65, or age less than 75 and not significantly compromised by comorbid conditions,
- Age greater than or equal to 75, or less than 75 but significantly compromised by comorbid conditions.

Evidence of objective impairment using the following features: 1) FVC < 65%, 2) Desaturation with exertion (PaO_2 < 88% on room air), 3) $D_{Lco} \leq 50\%$

- Mild impairment = none of the three features
- Moderate impairment = any one of the features
- Severe impairment = 2 or 3 of the features

Prior failed therapies

- No prior steroids or cytotoxic agents
- Prior steroids
- Prior cytotoxic agents (i.e. azathioprine or cyclophosphamide)
- Prior steroids and cytotoxic agents

Treatment options considered

- No treatment
- Corticosteroids alone
- Azathioprine + corticosteroids
- Cyclophosphamide + corticosteroids
- Interferon gamma-1b alone
- Interferon gamma-1b + corticosteroids
- Pirfenidone
- Referring patients for enrollment in randomized trials
- Referring patients for transplant evaluation

Table II

Appropriateness of various treatments for IPF by age and severity subgroups

	No Treatment	*Steroids alone*	*Azathioprine + Steroids*	*Cyclophos + Steroids*	*IFN*	*IFN + Steroids*
< 65, mild						
No prior steroids or cytotoxic agents	−	−	+	0	0	0*
Failed prior steroids	−	−	+	0	+	0
Failed prior cytotoxic agents	−	−	0	−	+	+
Failed prior steroids and cytotoxic agents	0*	−	−	−	+	+
< 65, moderate						
No prior steroids or cytotoxic agents	−	−	+	0	0*	0*
Failed prior steroids	−	−	0	0	+	0
Failed prior cytotoxic agents	−	−	0	−	+	+
Failed prior steroids and cytotoxic agents	−	−	−	−	+	+
< 65, severe						
No prior steroids or cytotoxic agents	−	−	0	0	−	0
Failed prior steroids	−	−	0	0	0*	0
Failed prior cytotoxic agents	0*	−	−	−	0*	0
Failed prior steroids and cytotoxic agents	0*	−	−	−	0*	0
65–79, mild						
No prior steroids or cytotoxic agents	−	−	0	−	0	0*
Failed prior steroids	0	−	0*	−	+	0
Failed prior cytotoxic agents	0*	−	−	−	0	0
Failed prior steroids and cytotoxic agents	0*	−	−	−	+	0
65–79, moderate						
No prior steroids or cytotoxic agents	−	−	0	−	0	0*
Failed prior steroids	−	−	0*	−	+	0
Failed prior cytotoxic agents	0*	−	−	−	+	0
Failed prior steroids and cytotoxic agents	0*	−	−	−	+	0
65–79, severe						
No prior steroids or cytotoxic agents	0*	−	0*	−	−	−
Failed prior steroids	0*	−	0*	−	−	0
Failed prior cytotoxic agents	0*	−	−	−	−	0
Failed prior steroids and cytotoxic agents	0*	−	−	−	0	0

* 0 = panelist disagreement

+ = Appropriate, − = Inappropriate, **0** = Uncertain, **Steroids** = Corticosteroids, **Cyclophos** = Cyclophosphamide

Table III

Appropriateness of selected other therapeutic options in IPF by age

	Pirfenidone	*Refer for randomized trial*	*Refer for Transplant*
Age < 65	Uncertain	Appropriate	Appropriate
Age ≥ 65	Uncertain	Appropriate	Inappropriate

Table IV

Studies included in systematic literature review provided to panelists

Author, Year	*Comparison*	*Type*	*N*	*Average follow-up*	*Comments*
Ziesche 1999 [16]	IFN + prednisolone vs. prednisolone	RCT*	18	12 months	Excellent¶ RCT showed statistically significant improvement in 18 confirmed IPF patients treated with INF gamma-1b vs. steroids alone.
Raghu 2004 [15]	IFN + steroids vs. placebo + steroids	RCT	330	14 months	Excellent RCT showed considerable survival benefits in secondary analyses only for patients with confirmed IPF patients treated with INF gamma-1b relative to placebo.
Antoniou 2002 [17]	INF vs. colchicine + prednisone	RCT	27	6 months	RCT reported in abstract form with 27 IPF patients, found IFN arm had 50%, 40%, and 10% who were improved, stable and worse respectively at 6 months compared to 0%, 60%, and 40% in the colchicine + prednisone arm. At 11 months no deaths in IFN arm, 2 in control arm.
Turner-Warwick 1980 [9]	Prednisolone vs. control	CC	220	4–14 years	Poor quality CC study, not confirmed IPF, showed no improvement with steroids.
Douglas 2000 [18]	Colchicine vs. prednisone *vs.* both *vs.* no treatment	CC	487	~ 4.5 years	Good quality retrospective cohort study, confirmed IPF, showed no therapy was not different from colchicine, prednisone or both for survival.
Douglas 1998 [19]	Prednisone *vs.* colchicine	RCT	26	1.5 years (median)	Excellent RCT, confirmed IPF, showed no clinical or survival difference between high dose steroids and colchicine, with considerable steroid toxicities.
Raghu 1991 [14]	Azathioprine + prednisone *vs.* placebo + prednisone	RCT	27	up to 9 years	Excellent RCT, confirmed IPF, showed no clinical improvement with azathioprine + steroids over steroids alone but marginally significant improved survival, no significant toxicities.
Winterbauer 1991 [20]	Prednisone + azathioprine *vs.* prednisone + placebo	RCT	27	up to 12 months	Brief report of RCT, unclear definition of IPF in 27 patients, showed trend toward clinical improvement with azathioprine + steroids over steroids alone, with considerable toxicities attributable to steroids.
Gay 1998 [21]	Cyclophosphamide + high dose prednisone (HDP) *vs.* HDP responders	RCT	66	up to 39 months	Good cohort study, confirmed IPF, showed that patients who did not respond initially to steroids fared worse, and only HRCT imaging and pathologic fibrosis predicted survival.
Johnson 1989 [22]	Cyclophosphamide + low dose prednisolone *vs.* HDP	RCT	43	5+ years	Good RCT, 43 unconfirmed IPF patients, showed no clinical improvement with cyclophosphamide + steroids over steroids alone but cyclophosphamide may have a steroid-sparing effect, or that low = high dose steroids with no help from cyclophosphamide, with some reversible toxicities.
Selman 1998 [23]	Prednisone vs. pred. + colchicine *vs.* pred. + D-penicillamine *vs.* all three	Coh	56	> 5 years	Good quality prospective cohort study, confirmed but advanced IPF, showed prednisone alone was not different after adding colchicine, D-Penicillamine or both, with many adverse effects from steroids.

*RCT = randomized controlled trial, CC = case-control study, Coh = cohort study

¶Study quality ratings correspond to those of the Oxford Center for Evidence-based Medicine, with “Excellent” = 1a, “Good” = 1b or

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