Methotrexate and Injectable Tumor Necrosis Factor-α Inhibitor Adherence and Persistence in Children with Rheumatic Diseases

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ABSTRACT. ***Objective.*** To measure adherence and persistence with methotrexate (MTX) and injectable tumor necrosis factor-α (iTNF-α) inhibitors (etanercept, adalimumab) among children prescribed these medications by a rheumatologist.

Methods. Data were obtained from a US pharmacy benefits management firm. Children were included if they were < 18 years of age, had ≥ 1 prescription claim between January 2009 and December 2010 for MTX or an iTNF-α inhibitor that was prescribed by an adult or pediatric rheumatologist. The medication possession ratio (MPR) was calculated for each medication, with MPR ≥ 80% indicating good adherence. MPR were compared by route of administration, age, and by new users versus continuing users. Persistence was measured for new users of each medication from initiation until discontinuation, or for a maximum of 1 year.

Results. A total of 1964 children were included. The majority of children had MPR < 80%. Children taking subcutaneous MTX had the lowest mean MPR [46.9%; median 44.9%; interquartile range (IQR) 23%–69.6%] and the lowest persistence, with 26% of children continuing the medication at 1 year. Mean MPR was highest for iTNF-α (65.7%; median 70.1%; IQR 46%–89.3%), as was persistence, with 52% of children continuing the medication at 1 year. Children age < 13 years tended to have higher MPR, but this was statistically significant only for oral MTX (61.1% vs 54.9% in children age ≥ 13 yrs; p = 0.02).

Conclusion. Adherence and persistence in this cohort varied by medication and route of administration. Both outcomes are important considerations for physicians prescribing these medications in routine clinical care and for the assessment of treatment effectiveness in the research setting. (J Rheumatol First Release Nov 1 2012; doi:10.3899/jrheum.120753)

Key Indexing Terms:
TUMOR NECROSIS FACTOR INHIBITOR
METHOTREXATE
PEDIATRIC RHEUMATIC DISEASES
PATIENT COMPLIANCE

Medication adherence, the degree to which patients follow a prescribed treatment protocol, has important implications for treatment effectiveness, cost, and safety[1]. It is estimated that reduced adherence to medications may lead to $100 billion in unnecessary healthcare spending each year[2]. Medication persistence (the time between initiation and discontinuation of a medical therapy) is a separate concept from adherence but has similarly important effects on outcomes[3]. Reduced adherence and reduced persistence can both lead to unnecessary escalations in treatment that may result in increased healthcare use, suboptimal disease control, and unfavorable patient outcomes. These outcomes are of particular significance because clinical research increasingly focuses on the measurement of comparative treatment effectiveness (treatment effects in the setting of routine clinical care) in contrast to efficacy (treatment effects within the setting of clinical research).

Pediatric rheumatic diseases, the most common of which is juvenile idiopathic arthritis (JIA), currently affect about 300,000 children in the United States, accounting for 827,000 ambulatory visits per year[4]. Given the chronicity of these diseases, children with rheumatic diseases are often expected to take medications for long periods, are likely to experience medication side effects, and are frequently treated with complex medication regimens. All these factors have been shown to reduce adherence[5,6,7]. Medication adherence among children and adolescents is particularly

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Supported by grant K12HS019482 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

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Accepted for publication September 26, 2012.

challenging because family interactions and the child's developmental stage can significantly affect it[6,8].

Methotrexate (MTX) is one of the most commonly prescribed medications for JIA and data support its use as a first-line agent for certain forms of JIA[9,10]. Two injectable tumor necrosis factor-α (iTNF-α) inhibitors, etanercept and adalimumab, are approved by the US Food and Drug Administration for use in JIA, and recent data suggest that the prevalence of anti-TNF-α medication for JIA is now approaching that for adult rheumatoid arthritis (RA)[11]. While JIA is the most common indication for these medications, they are also used in the treatment of additional rheumatic and inflammatory conditions, including iritis, sarcoidosis, psoriasis, and inflammatory bowel disease[12,13,14]. Despite their frequent use and established efficacy in clinical trials, few data regarding children's adherence and persistence with these medications have been published, with estimated adherence ranging from 50% to 80%, primarily because of the lack of datasets with sufficient numbers of patients[15,16]. Pharmacy benefit management firms (PBM) provide a unique source of pharmacy claims data with which to assess these outcomes.

The objectives of these analyses were to use data from a large PBM to assess adherence and persistence with MTX and iTNF-α among children prescribed 1 or more of these medications by an adult or pediatric rheumatologist, and to estimate the association between patient factors, including sex and age, with adherence.

MATERIALS AND METHODS

The study cohort was constructed from claims data provided by CVS Caremark®, a PBM with about 45 million beneficiaries in the United States. Available data included provider specialty, start and end dates for each medication claim, dates of medication fills, route of medication administration, and demographic data including patient age, sex and insurance status. Medical claims, including diagnosis codes, are not represented in this database. Children were included in the cohort if they had at least 1 claim for an iTNF-α or MTX that was prescribed by a pediatric or adult rheumatologist in the CVS Caremark database between January 1, 2009, and December 31, 2010. Children were also required to have 6 months of eligibility before their first iTNF-α or MTX claim in 2009, a minimum of 12 months of eligibility within the PBM, and be < 18 years of age at the time of the claim. Duplicate or overlapping claim days were not counted as therapy days. Each patient could have at most 365 days of therapy, out of 365 days eligible. Children were excluded if they had a medical claim for an infused biologic agent (i.e., infliximab, abatacept, rituximab), because medical claims are not consistently represented within the PBM. Children with incomplete or missing date of birth data were also excluded. Human subject approval and ethics approval were obtained from the Seattle Children's Hospital institutional review board. All individually identifiable health information was protected in accord with US federal and state laws.

Medication exposure categories. Eligible children were grouped into the following categories: (1) iTNF-α (children with ≥ 1 claim for an iTNF-α, with or without concomitant MTX); (2) MTX in combination with an iTNF-α; and (3) MTX monotherapy (children with ≥ 1 claim for MTX and no claims for an iTNF-α). Children were considered to be receiving combination therapy if they had ≥ 30 days of overlap of claims for the medications of interest. Children in the MTX monotherapy group were further classified by whether they were receiving oral or subcutaneous MTX. iTNF-α inhibitor monotherapy was not examined as a separate group because those medications are frequently used in conjunction with MTX, particularly early in treatment, and it was hypothesized that the combination group would most closely reflect current clinical practice.

Medication adherence. Medication adherence was calculated as the medication possession ratio (MPR) — the number of days of medication dispensed to the child divided by the number of days the child would have been expected to take the medication based on the prescription duration. Expected duration of each claim was calculated based on the dispense date and duration of each claim. Patients with a gap of ≥ 60 days for the medication, or no additional claims for the medication of interest, were considered discontinued from the medication of interest at the end date of their last claim for the medication and censored from the dataset at that point. An MPR of 100% indicated that the child's medication was refilled as prescribed, while an MPR < 100% indicated that the medication was refilled less frequently than prescribed. The MPR has been used as a surrogate for adherence in a number of different settings. In general, an MPR ≥ 80% indicates good adherence, while an MPR < 80% is considered poor adherence[17].

To identify whether the patient characteristics available in the claims data were associated with medication adherence, MPR was also calculated for the cohort by sex and age. Age was dichotomized into < 13 years versus ≥ 13 years, as we hypothesized that adherence would differ for older children, who would be expected to have more autonomy over their medications[8]. Adherence was also assessed between patients who were taking MTX as monotherapy versus MTX in combination with an iTNF-α, to determine whether complexity of treatment regimen was associated with differential compliance. MPR was also assessed by route of administration (oral vs subcutaneous) for MTX. To determine whether medication adherence differed between new users (treatment initiators) versus children who were continuing users of the medication of interest, children were defined as treatment initiators if they had no prior claims for the medication of interest for the 6 months prior to their first claim for the medication and remained in the cohort for at least 1 year following this initial claim, to ensure that the claim represented a new medication for the child and that adequate followup was available. Otherwise, children were classified as continuing users.

Days without therapy were also calculated because the MPR may overestimate adherence during the first few months of a new medication. Days without therapy measured the number of days for which the patient did not have medication over their first year of the medication. For each claim in the eligibility period, the number of days of medication dispensed was summed for each patient to calculate the total number of expected therapy days. Days without therapy were then calculated as 365 minus therapy days for each patient.

Medication persistence. Medication persistence was calculated for initiators of iTNF-α and MTX as the percentage of children still taking the medication of interest following their first claim for the medication and over the subsequent 365 days. As with the MPR calculations, patients were considered discontinued from the medication of interest at the end date of their last claim for the medication.

Statistical analyses. Descriptive statistics were generated for children in the cohort receiving any of the 3 medications of interest, including MTX as either monotherapy or combination therapy. Unpaired t-tests were used to compare mean MPR. Analyses were performed using SAS version 9.2.

RESULTS

The analysis included 1964 patients (Table 1). The majority of children (n = 1039; 53%) received MTX monotherapy. The cohort was predominantly female and the majority of prescriptions (78%–94%) were from pediatric rheumatolo-

Table 1. Patient characteristics (n = 1964). Data are n (%).

Characteristic	Medication(s)			
	iTNF-α, n = 773	MTX Comb, n = 534	MTX Mono, n = 1039	Total, n = 1964
Age, yrs				
0–8	163 (21)	142 (27)	329 (32)	540 (27)
9–12	201 (26)	142 (27)	286 (28)	523 (27)
13–16	233 (30)	153 (29)	285 (27)	566 (29)
> 16	176 (23)	97 (18)	139 (13)	335 (17)
Sex				
Female	509 (66)	382 (72)	741 (71)	1361 (69)
Region (US)				
Midwest	173 (22)	132 (25)	246 (24)	460 (23)
Northeast	183 (24)	128 (24)	233 (22)	460 (23)
South	291 (38)	196 (37)	372 (36)	711 (36)
West	112 (14)	69 (13)	164 (16)	291 (15)

iTNF-α: injectable tumor necrosis factor-α inhibitor (etanercept or adalimumab) alone or in combination with methotrexate; MTX Comb: methotrexate in combination with iTNF-α; MTX Mono: MTX without concomitant iTNF.

gists. More than 80% of children in this cohort had private insurance.

Medication adherence. For each medication category, the majority of children had MPR < 80% (Table 2). The subcutaneous MTX monotherapy group had the smallest percentage of children with MPR ≥ 80% (14.5%) and the highest mean number of days without therapy (193.9). The iTNF-α inhibitor group had the largest percentage of children with MPR ≥ 80% (38.4%) and the lowest mean number of days without therapy (125.2). The mean MPR for the cohort ranged from 46.9% (median 44.9%; IQR 23%–69%) for children receiving subcutaneous MTX

Table 2. Medication adherence summary.

Medication	N	Mean Therapy Days	Mean Days without Therapy	MPR (%) Mean, median (IQR)	MPR ≥ 80%, n (%)	p
iTNF-α	773	239.8	125.2	65.7, 70.1 (46.0, 89.3)	297 (38.4)	
Age < 13	364	246.8	118.2	67.6, 72.1 (46.3, 91.1)	150 (41.2)	
Age ≥ 13	409	233.6	131.4	64.0, 69.0 (46.0, 87.7)	147 (35.9)	0.055
Male*	263	239.8	125.2	65.7, 70.7 (46.0, 89.6)	105 (39.9)	
Female	509	240.2	124.8	65.8, 70.1 (46.0, 89.0)	192 (37.7)	0.958
MTX in combination with iTNF-α	534	197.0	168.0	54.0, 55.8 (31.5, 74.8)	109 (20.4)	
Age < 13	284	200.8	164.2	55.0, 57.1 (34.0, 75.6)	59 (20.8)	
Age ≥ 13	250	192.8	172.2	52.8, 53.7 (30.7, 74.2)	50 (20.0)	0.336
Male*	151	192.8	172.2	52.8, 52.6 (32.9, 74.0)	27 (17.9)	
Female	382	199.0	166.0	54.5, 57.8 (31.2, 75.9)	82 (21.5)	0.505
MTX monotherapy	1039	201.9	163.1	55.3, 58.1 (30.7, 79.7)	256 (24.6)	
Age < 13	615	205.9	159.1	56.4, 59.7 (32.9, 80.0)	154 (25.0)	
Age ≥ 13	424	196.1	168.9	53.7, 54.1 (27.8, 79.6)	102 (24.1)	0.127
Male	298	200.9	164.1	55.1, 59.5 (29.9, 79.5)	71 (23.8)	
Female	741	202.3	162.7	55.4, 58.1 (30.7, 79.7)	185 (25.0)	0.846
Oral MTX monotherapy	489	210.8	154.2	57.7, 61.9 (30.7, 83.8)	145 (29.7)	
Age < 13	225	223.0	142.0	61.1, 68.8 (38.4, 86.0)	79 (35.1)	
Age ≥ 13	264	200.3	164.7	54.9, 57.3 (27.7, 80.1)	66 (25.0)	0.018
Male	150	206.9	158.1	56.7, 60.8 (29.9, 84.1)	42 (28.0)	
Female	339	212.5	152.5	58.2, 64.4 (30.7, 83.8)	103 (30.4)	0.592
Subcutaneous MTX monotherapy	303	171.1	193.9	46.9, 44.9 (23.0, 69.6)	44 (14.5)	
Age < 13	235	175.3	189.7	48.0, 47.7 (25.5, 69.3)	32 (13.6)	
Age ≥ 13	68	156.6	208.4	42.9, 32.7 (15.3, 75.5)	12 (17.6)	0.171
Male	83	168.5	196.5	46.2, 48.8 (16.4, 71.2)	11 (13.3)	
Female	220	172.1	192.9	47.1, 44.7 (24.7, 69.2)	33 (15.0)	0.784

* Missing sex data for 1 patient. MPR: medication possession ratio; iTNF-α: injectable tumor necrosis factor-α inhibitor (etanercept or adalimumab) alone or in combination with methotrexate; MTX: methotrexate.

monotherapy to 65.7% (median 70.1%; IQR 46%–89.3%) for children receiving an iTNF-α. The mean MPR for MTX were not significantly different between the MTX monotherapy group and the combination MTX/iTNF-α group (55.3% and 54%, respectively; p = 0.36). However, the mean MPR were significantly higher for oral MTX in comparison to subcutaneous MTX monotherapy groups (57.7% and 46.9%, respectively; p < 0.001).

The mean MPR for children < 13 years of age receiving oral MTX monotherapy was 61.1%, which was significantly higher than that of children age ≥ 13 years (54.9%; p = 0.02). These children also had a lower mean number of days without therapy than the children age ≥ 13 years. Children age < 13 years also had a higher mean MPR for iTNF-α than children ≥ 13 years and a lower mean number of days without therapy, but this difference did not reach statistical significance (67.6% and 64%, respectively; p = 0.055). There were no other statistically significant differences in mean MPR between either sex or age groups, although there was a trend toward children < 13 years of age having higher MPR and lower mean days without therapy for each of the medication categories.

The MPR were significantly higher for continuing users of MTX monotherapy as compared to initiators, regardless of the route of administration (Table 3). There was no difference in mean MPR for continuing users versus initiators of iTNF-α, or for MTX when prescribed in combination with iTNF-α.

Medication persistence. Medication persistence for new users of each medication combination is summarized in Figure 1. At 6 months after initiation, 75% of children receiving iTNF-α were persistent with the medication, 57% of children receiving oral MTX continued receiving the medication, and 42% of children receiving subcutaneous MTX continued receiving the medication. The iTNF-α group also had the highest persistence at 1 year, with 52% of children continuing to receive an iTNF-α after 12 months. In comparison, only 37% of children still received oral MTX and 26% of children still took subcutaneous MTX after 12 months. Patients taking oral MTX had higher persistence than those taking subcutaneous MTX throughout the 12-month period.

DISCUSSION

The objectives of our analysis were to estimate adherence to MTX and iTNF-α inhibitors, medications commonly used in the treatment of pediatric rheumatic diseases, using data from a large PBM. The results of this analysis provided novel information about medication adherence in a large cohort of children receiving care from an adult or pediatric rheumatologist.

Several important trends were noted. First, these data suggest that adherence and persistence are particularly low for subcutaneous MTX, possibly because of a differential side effect pattern. Children > 13 years of age tended to have lower adherence, possibly because of less parental involvement in medication administration, denial of their underlying illness, and/or negative feelings toward their illness or healthcare providers, as has been reported for adolescents with other chronic diseases[8,10,18,19]. However, this dif-

Table 3. Medication adherence for initiators and continuing users.

Medication	N	Mean Therapy Days	Mean Days without Therapy	MPR (%) Mean, median (range), (IQR)	MPR ≥ 80%, n (%)	p
iTNF-α						
Initiators	304	242.4	122.6	66.4, 71.0 (7.7, 100.0), (46.0, 92.5)	128 (42.1)	
Continuing users	469	238.2	126.8	65.2, 69.3 (7.7, 100.0), (46.0, 87.7)	169 (36.0)	0.5410
MTX in combination with iTNF-α						
Initiators	242	194.7	170.3	53.3, 54.4 (1.6, 99.2), (30.7, 76.2)	53 (21.9)	
Continuing users	292	199.0	166.0	54.5, 55.9 (1.9, 100.0), (34.5, 74.0)	56 (19.2)	0.6124
MTX monotherapy						
Initiators	467	190.9	174.1	52.3, 54.5 (1.9, 100.0), (23.6, 79.7)	114 (24.4)	
Continuing users	572	210.9	154.1	57.8, 61.4 (5.5, 100.0), (35.8, 79.7)	142 (24.8)	0.0015
Oral MTX monotherapy						
Initiators	227	197.4	167.6	54.1, 59.5 (2.7, 98.9), (23.0, 83.8)	69 (30.4)	
Continuing users	262	222.4	142.6	60.9, 66.8 (7.7, 100.0), (41.1, 84.1)	76 (29.0)	0.0090
Subcutaneous MTX monotherapy						
Initiators	152	159.4	205.6	43.7, 39.5 (1.9, 99.7), (16.4, 69.6)	22 (14.5)	
Continuing users	151	182.9	182.1	50.1, 49.9 (5.5, 97.5), (30.7, 69.6)	22 (14.6)	0.0391

MPR: medication possession ratio; iTNF-α: injectable tumor necrosis factor-α inhibitor (etanercept or adalimumab) alone or in combination with methotrexate; MTX: methotrexate.

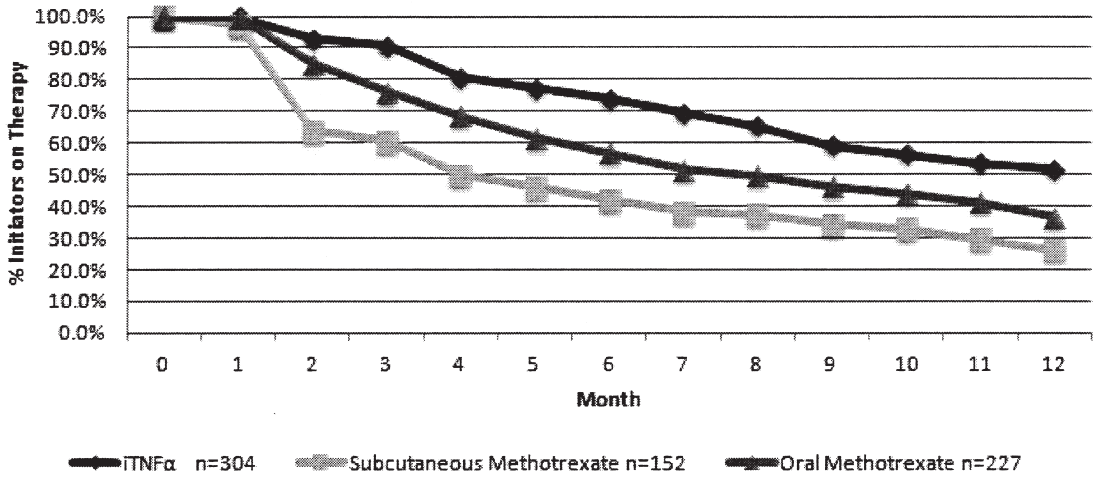

Figure 1. Medication persistence among treatment initiators. iTNF-α: injectable tumor necrosis factor-α inhibitors (etanercept or adalimumab) alone or in combination with methotrexate.

ference reached statistical significance only for children receiving oral MTX. Continuing users of MTX also had improved adherence as compared to new users, regardless of route of administration. This difference may reflect that children who respond well to a medication and have few side effects are more likely to continue it[20].

Medication adherence in children and adults with chronic disease has been estimated at about 50%, and varies significantly depending on the method used to assess adherence[21,22]. Medication adherence in JIA specifically has been estimated by a number of measures including electronic monitoring devices, surveys of patients, parents and physicians, and by serum drug assays. Studies using parent-reported and/or patient-reported measures of adherence have tended to report higher rates of adherence than other, more objective measures. For example, a recent cross-sectional survey of 76 children with JIA estimated that about 83% of children received ≥ 80% of their prescribed MTX, based on parent response to a questionnaire that dichotomized children by whether they received at least or less than 80% of their prescribed doses[16]. Studies that have measured adherence using the Parent Adherence Report Questionnaire, a standardized measure of medication adherence, have reported similar medication adherence rates in children with JIA (86.1%–90.4%)[23,24]. Alternatively, a study that used an electronic monitoring device to assess adherence to a daily nonsteroidal antiinflammatory drug (NSAID) for 4 weeks in 48 children with newly diagnosed juvenile arthritis found that only about 50% of children were adherent with this medication[25]. A small study that measured adherence to aspirin using serum salicylate assays also reported about 50% adherence[15]. The analyses in our report suggest that adherence with MTX and/or an iTNF-α inhibitor is somewhat higher than for the daily NSAID, as measured by serum levels, but significantly lower than the parent-reported data.

To our knowledge, this is the first report in pediatric rheumatic diseases to use the MPR as an indicator of medication adherence. The MPR has been used to estimate adherence in other pediatric chronic diseases, including asthma and attention deficit disorder, which have calculated MPR ranging from 15% to 52% based on Medicaid prescription claims data[26,27,28]. The MPR has also been used to estimate adherence for adults with RA. The MPR for MTX in adults with RA have been estimated at about 59%, somewhat higher than the findings in our current study[29]. The MPR for iTNF-α in adults have been reported to be 63%–70%, with continuing users tending to have higher MPR, consistent with our findings for iTNF-α in children[30].

A primary limitation to the use of PBM data is the lack of diagnostic codes, medical claim data, and additional patient-level data. Because diagnostic codes were not available, we were unable to determine the indication for each of these medications. Although JIA is likely to account for the majority of prescriptions for both MTX and iTNF-α, the use of these medications for other inflammatory diseases cannot be excluded and may have altered the results. Further, because of this lack of patient-level data, we were also unable to perform propensity scoring analyses or use other techniques to control for confounding that exists in such observation datasets. We were also not able to assess whether medications dispensed to patients were actually administered or whether medication dosages were changed after the medication was dispensed. In the case of liquid MTX, for which the doses are more variable and the actual volume of medication dispensed may be determined by standard vial sizes rather than the supply requested by the provider, our MPR estimates may have been affected by the

lack of specific dose data. However, we anticipate that pharmacies nevertheless supply the vial size that most closely approximates the volume the family needs and therefore in most cases the MPR should remain ≥ 80%. Further, we did not assess all claims for concomitant disease-modifying antirheumatic drug claims or the complexity of the overall regimen, which may have affected adherence. While these data suggest that route of administration and age may be associated with decreased adherence, we were not able to adjust for disease activity, JIA category, and other potential confounders. Similarly, we were not able to assess the reasons for lower adherence or persistence, because data regarding adverse events, medication refills outside the system, and/or medication switching were not available. Further, the majority of children (> 85%) in this dataset had private insurance, and the small numbers of children with public insurance limited a comparison between the 2 groups. Prior reports have suggested that higher socioeconomic status is associated with improved adherence, and it may be that the data in this report have therefore overestimated MPR[31].

The overall low MPR in this cohort and variable persistence suggest that it is important to account for both of these factors in determining the effectiveness of these medications in routine clinical care and in the research setting. Additional assessments in more heterogeneous cohorts of patients may better identify children most likely to have decreased adherence and those who are most likely to benefit from specific adherence interventions. Similarly, additional measurements of these outcomes in datasets with more detailed clinical information will be important in determining the effect of these factors on additional outcomes, including disease activity and healthcare costs.

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