Sustainability and switching of biologics for psoriasis and psoriatic arthritis at Fukuoka University Psoriasis Registry

Biologics used to treat psoriasis

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Abstract

Biologics are efficacious for treating psoriasis vulgaris (PsV) and psoriatic arthritis (PsA), but sometimes must be terminated or changed for various reasons including ineffectiveness or adverse events. To find the optimal choice of biologics for treating psoriasis, we analyzed the real-world data on drug survival and the reason for terminating or switching biologics. Medical records from patients with PsV or PsA, who visited the Department of Dermatology, Fukuoka University Hospital from 2010 to 2017, were analyzed. Two hundred and eleven patients received biologics, and 147 patients (69.7%) were treated with only one biologic, while 64 patients (30.3%) were switched to different products. Frequently used biologics in PsV were ustekinumab (UST), infliximab and adalimumab when calculated by patient-year. Tumor necrosis factor inhibitor (TNFi) use decreased while UST and interleukin (IL)-17 inhibitors increased in newly introduced patients. UST showed the highest survival rate as a first-line drug, but the advantage was lost in the second reagent's group. The major reasons for terminating/switching biologics were as follows: primary ineffectiveness (26.4%), secondary loss of efficacy (36.5%), patient's preference, including referral to nearby hospital, or stopped visiting (22.6%), side-effects (7.7%), comorbidities (3.4%) and economic burden (2.4%). In PsA patients, TNFi are more frequently employed than in PsV patients, although switching to UST or IL-17 inhibitors showed an increasing trend. Biologic reagents were changed mostly because of primary or secondary loss of efficacy, which affected drug survival. Further research is needed to find the optimal choice of biologics with larger samples at multiple facilities.

Key words: biologics, inefficacy, psoriasis, switching, drug survival

Introduction

Psoriasis is a chronic inflammatory disease mainly affecting the skin and joints.[1,2] Although the exact cause of the disease has not been clarified, genetic pro-inflammatory predisposition as well as environmental factors are involved.[3,4]

Biologics were first approved for treatment of psoriasis in 2010 in Japan, and six

brands of biologics were available as of March 2017, all of which are highly effective. These biologics are classified into four classes according to their target molecules: inhibition against tumor necrosis factor (TNF)-α,[5,6] interleukin (IL)-12/23p40,[7,8] IL-17A[9,10] or IL-17 receptor A.[11] Each drug has its own characteristic efficacy, indications and side-effects. Based on these characteristics, dermatologists select brands for suitable patients.

However, in practice, there are some patients in whom biologics show little efficacy from the beginning, or in whom they lose their efficacy after successful induction for a certain period. Additionally, the efficacy is sometimes weakened when the original drug is re-administrated after a certain period during which administration of the medication is stopped. In such cases, administration of the original biologic may be terminated, or the patient may be switched to another biologic. The total value of a drug is judged by factors such as efficacy, safety, usefulness and economic burden. In clinical practice, a reliable index of the total value of a drug is a survival curve,[12] which is a continuous rate for each product. Thus, we surveyed patient survival for biologics and the reason for their discontinuation (termination or switch) in patients who visited Fukuoka University Hospital.

Methods

Patients

Among patients who visited the Department of Dermatology, Fukuoka University Hospital from 2010 to the end of 2017, patients who were diagnosed with psoriasis were registered in the Fukuoka University Psoriasis Patient Registry (FUPR). For the FUPR patients, clinical information (described below) was extracted from the medical records for all patients who received biologics after marketing approval was received for these medications. Biologics used in clinical trials were excluded. For analyses, patients with psoriatic arthritis (PsA) were independently analyzed from the rest of the psoriatic patients (psoriasis vulgaris, PsV). This study was approved by the internal review board of Fukuoka University Hospital.

Data extraction

The extracted information included the following: sex, age of onset, age at initial visit, body mass index, family history of psoriasis, clinical history, life history (smoking, drinking), disease phenotype (plaque psoriasis, psoriatic arthritis, pustular psoriasis or other forms), Physician's Global Assessment of severity, body surface area involvement and comorbidities (obesity, diabetes, hypertension, hyperlipidemia, hyperuricemia).

The beginning and final dates of biologic product administration were recorded. In patients with multiple biologics, all drugs were recorded. To analyze the longitudinal trend for biologics, we counted the number of patients who were given a certain brand of biologics each year (patient-year analysis). If a patient's drug was changed during a year, each drug was counted. For example, if one patient received two different drugs in 2017, each drug was counted as one in 2017. When a drug was discontinued (either terminated or switched to another drug), the reason was examined and classified into the following nine categories: (i) primary ineffectiveness for skin symptom; (ii) secondary loss of efficacy for skin symptom; (iii) primary ineffectiveness for joint symptom; (iv) secondary loss of efficacy for joint symptom; (v) side-effects; (vi) problems with self-injection; (vii) patient's preference (including referral to nearby hospitals and stopped attending visits in our department); (viii) economic burden; or (ix) remission. Additionally, for the first drug and the second drug, the survival period was examined using survival time analysis. Termination because of primary ineffectiveness, secondary loss of efficacy, side-effects or economic burden was judged as "event", while termination resulting from the patient's preference or remission was judged as "censored".

Statistical analyses

Microsoft Excel was used to compile the data. GraphPad Prism (GraphPad Software, CA, USA) was used for statistical analysis. Fisher's exact test and Student's t-test were performed to compare the ratio and the average value of two groups, respectively. For comparison of survival curves, the log–rank test was performed. $P < 0.05$ was regarded as a significant difference in all analyses.

Results

Profiles of patients

From January 2010 to December 2017, data from 211 psoriatic patients (158 men, 53 women; male-to-female ratio, 3.0), including patients with PsA who had received biologics, were analyzed. The medical history of the study group is shown in Table 1. The overall mean age at the first visit was 50 years (±15 years); the mean age for men was 49 years (±14 years) and that for women was 53 years (±17 years). The overall mean age of onset was 40 years (±17 years), while the mean age of onset for men was 39 years (±16 years) and that for women was 44 years (±21 years).

The frequency of psoriasis in families was 11.8% overall, and it was 10.1% for men and 16.9% for women. The smoking and the daily drinking habits in men were 50.6% and 38.6%, respectively, and those for women were 26.4% and 28.3%, respectively. The smoking rate in men was significantly higher than that of women (P = 0.002). For medical history/complications, tonsillitis was 6.6% overall, and 7.6% for men and 3.8% for women; cerebral infarction was seen in 2.4% overall, and 1.9% for men and 3.4% for women; and myocardial infarction was seen in 2.4% overall, and in 2.5% of men and 1.9% of women. PsA was present in 28.4% overall, and in 26.6% of men and 34% of women. Pustular psoriasis was present in 4.4% of men and 11.3% of women. Guttate psoriasis was only present in women, and 3.8% were affected. Erythroderma was present in men only, and 1.9% were affected.

Number of biologics used per year

The number of drugs used was determined per year using a patient-year analysis, as described above. Overall, the most frequently used biologics were ustekinumab (UST) (223 patient-years [PY]), adalimumab (ADA) (222 PY) and infliximab (IFX) (142 PY), followed by secukinumab (SEC) (110 PY), brodalumab (BRO) (33 PY) and ixekizumab (IXE) (12 PY) (Table 2, Fig. 1a). These results reflected those products that were released earlier. When stratified by the absence of PsA, UST (210 PY, P = 0.0001) was the most frequently used followed by ADA (183 PY), IFX (108 PY) and SEC (104 PY).

In patients with PsA, ADA (39 PY, P = 0.0467) was most frequently used, followed by IFX (34 PY), UST (13 PY), BRO (9 PY) and SEC (6 PY) (Table 2, Fig. 1b). When patients with or without PsA were compared, IFX and ADA were used significantly more frequently (P = 0.0002 and P = 0.0467, respectively), and UST, SEC and BRO were used

significantly less frequently (P = 0.0001, 0.0061 and 0.0328, respectively) in patients with PsA (Table 2).

Trends for biologics were also analyzed. Figure 2 shows the number and proportion of patients who received the specified brand during a year. Note that patients whose drug was changed in the middle of the year were counted for both drugs. For PsV patients, the number of patients using biologic products increased over the years, reaching 180 patients/year in 2017, which is six-times higher than in 2010 (Fig. 2a). As the number of medications increased, the proportion of one drug gradually decreased. Use of IFX and ADA, which were of the first biologic agents approved in Japan, decreased while that of UST and SEC increased (Fig. 2b).

A different tendency was seen in PsA patients (Fig. 2c). The number of patients using IFX and ADA gradually increased until 2017. TNF inhibitors (TNFi) were used two- to five-times more in PsA patients compared with PsV patients (Fig. 2c), but their use gradually decreased even in the PsA patient population (Fig. 2d).

Survival of biologic products

The continued duration of first-line and second-line biologics was examined using survival-time analysis. Among the 211 patients, the most used first-line drug was ADA, which was administrated to 71 patients (33.6%). The second most frequently used first-line drug was UST, which was administrated to 58 patients (27.5%). UST had the highest rate of continuous use until 2017 (50/58 patients; 86.2%) except for a few cases of IXE and BRO use. Among the second-line drugs, UST was again the most frequently used (24 patients), nine of whom were switched from IFX and 15 of whom were switched from ADA. No patients were switched to UST from IL-17 inhibitors.

The median survival of patients taking each first-line biologic product used was as follows: IFX, 35 months; ADA, 18 months; UST, 41 months; SEC, 34 months; IXE, 10 months; and BRO, 5 months. All drugs except IXE were administrated to patients who were switched from IFX and ADA; ADA was the most frequently used after IFX (10 patients) and UST was the most frequently used after ADA (15 patients). There were three cases of patients taking ADA and SEC who were switched from UST (Table 3).

The survival curve for patients taking first-line drugs is shown in Figure 3(a).

Patients taking UST had the highest survival rate. The median survival curves of patients taking UST were significantly larger than those of patients taking IFX and ADA (P = 0.0057 and 0.0005, respectively), but there was no statistically significant difference compared with SEC (P = 0.4724). Overall, the survival of any patient taking a second-line agent was poor. This observation supported the clinical observation that the second reagent was also often ineffective unless the first agent was effective. Although the sample size was small for PsA patients, there were many patients in whom both IFX and ADA were continued for a long time (Fig. 3c).

Discontinuation of biologics

Among the 211 patients treated with biologics, 147 (69.7%; 112 men, 35 women) were treated with only one biologic product. Eighty-five patients continued taking the first-line drug by the end of this survey, while use of the first-line drug was terminated and no other biologic products were used in 62 patients. The other 64 patients (46 men [71.9%], 18 women [28.1%]) were switched to other biologic products. Two products were administrated to 37 patients: three, four, five and six products were used in 18 patients (8.5% of the total), five patients (2.4% of the total), five patients (2.4% of the total) and one patient (0.5% of the total), respectively (Fig. 4).

Reasons for all drug discontinuations

We examined the reasons for discontinuing drugs (total, 208 times) in 126 patients, including 62 patients whose drug was terminated with the first drug and 64 who were switched to a second drug. The reasons for discontinuation of drugs were as follows: primary ineffectiveness in 55 patients (26.4%), secondary loss of efficacy in 76 patients (36.5%), patient preference (including patients stopped attending hospital visits and referral to a nearby hospital) in 47 patients (22.6%), side-effects in 16 patients (7.7%), unrelated comorbidities in seven patients (3.4%), economic burden in five patients (2.4%), problem with self-injection in one patient (0.5%) and remission in one patient (0.5%) (Fig. 5a). Primary ineffectiveness and secondary loss of efficacy accounted for more than 60% in all drugs. Side-effects of IFX were relatively high, accounting for 20% of the reasons for discontinuation. Self-injection was an issue for ADA and SEC, and referral to a nearby

hospital was relatively frequent. IXE and BRO were used in a small number of patients, so the results for these biologics were difficult to evaluate (Table 4, Fig. S1).

Reasons for terminating first biologics

Among 211 patients, 85 (40.3%) continued taking the first drug. In 62 patients (29.4%), the first-line drug was terminated without switching to another biologic. Among these 62 patients, 16 (25.8%) were referred to other hospitals, 16 (25.8%) stopped attending hospital visits without notice, eight (12.9%) were primarily ineffective and no further biologic reagents were introduced, and nine (14.5%) lost efficacy and non-biologic treatments were used. Five patients (8.1%) were discontinued because of the economic burden. Five patients (8.1%) were discontinued because of a comorbidity, gastric cancer, bone marrow transplantation scheduled for a blood disorder, pregnancy, dementia and liver enzyme elevation (Fig. 5b). All patients taking IFX were switched to other drugs and no termination was observed by primary ineffectiveness or lost efficacy. On the other hand, in approximately 30% of patients taking ADA and UST, there were patients whose biologic was terminated because of primary ineffectiveness or lost efficacy (Table 4).

Reasons for switching biologics

In 64 patients (30.3%), the first-line biologic was switched to another biologic at least once. The reasons for this switch were primary ineffectiveness to the skin symptoms in 20 patients (31.3%), and secondary loss of efficacy to the skin in 32 patients (50%). These two accounted for over 81.3% of reasons for discontinuation. In nine patients (14.1%), switching was caused by side-effects. A preference for visiting frequency, associated conditions and economic burden required switch in one patient each (1.6%, respectively; Fig. 5c).

When all drugs used in these 64 patients were tracked by counting one patient with one drug as “one time”, drug administration was observed 188 times; among these administrations, 42 (22.3%) were continued, while 146 (77.7%) were terminated. Patients treated with the highest numbers of drugs used all of the six available biologic products during the study period. The reasons for drug discontinuation were as follows: primary ineffectiveness in 39 patients (26.7%); secondary loss of efficacy in 70 patients (47.9%);

side-effects in 15 patients (10.3%); patient's preference and did not return for a visit in 16 patients (11%); remission and comorbidity in two patients (1.4%); problem with self-injection in one patient (0.7%); and economic burden in one patient (0.7%). IFX and ADA showed more secondary loss of efficacy compared with primary ineffectiveness, while for UST, 62% of patients experiencing primary ineffectiveness accounted for switching biologics, which may explain the low amount of secondary loss of efficacy in UST (Table 4).

Reason for discontinuation in PsA patients

Biologics were used for 27 of the 55 patients with arthritis and the remaining 28 patients received other treatments. Of the patients with biologics, 10 (37.0%) continuously took the first drug. The remaining 17 (63.0%) had their initial drug administration discontinued, and a total of 23 doses of these biologics were administrated. The most frequent reasons for discontinuation were primary inefficacy for the joint symptoms in eight patients (34.8%) and secondary loss of efficacy in eight patients (34.8%). Three patients (13.0%) stopped attending visits, two (8.7%) discontinued treatment because of an associated disease, and one (4.3%) had side-effects and self-injection difficulties (Fig. 5d).

In PsA patients, IFX and UST showed more primary ineffectiveness. Additionally, side-effects were often seen in IFX. However, secondary loss of efficacy was the most frequent reason for discontinuation in patients taking ADA (Fig. S2).

Discussion

Although dermatologists and rheumatologists currently have several choices of biologics, the optimal treatment against psoriasis has not yet been determined. In recent years, survival of patients taking biologics has been studied. Van den Reek et al.[12] reported the strengths and weaknesses of this type of study, but the survival rate can be considered to be an evaluation that shows the comprehensive usefulness of these drugs. There has been no research in Japan that examined the details of transitions in biologic administration to psoriatic patients and the reasons for terminating or switching between multiple biologics.

In this study, we showed an increasing trend for UST and IL-17 inhibitors and a decreasing trend for TNFi in the treatment of PsV patients. We also found that UST was

associated with better survival, which is similar to previous research.[13–15] Biologics were terminated mostly for two reasons: the patient's preference (referral to a nearby facility or patients not returning for visits) and primary or secondary ineffectiveness. However, switching of biologics was determined by a secondary loss of efficacy, followed by primary ineffectiveness and side-effects. For PsA patients, TNFi were still administrated most frequently, but there was no difference in drug survival compared with other products.

A variety of biologics for PsV became available recently, and newer drugs generally have better efficacy without an increase in side-effects.[16–24] .This led to increased use of the newer drugs with the expectation of better improvement of the skin symptoms. Worldwide, the survival rate of patients taking UST is higher than that of patients taking IFX and ADA.[13–15] Honda et al.[15] in Japan also reported that patients taking UST showed better survival compared with those taking other biologics, although survival analysis was not used in their research. Our survival analysis again confirmed the superiority of UST. Although there were not so many discontinuations, reasons for discontinuing UST were mainly primary ineffectiveness and secondary loss of efficacy, but there were few side-effects. We also found that there were a few patients in whom joint symptoms worsened during treatment in UST.

Similarly, SEC had few side-effects. However, patients taking SEC showed a decrease in survival rate after 2 years (Fig. 3a). This may be possibly because emergence of newer IL-17 inhibitors, IXE and BRO, in 2017. Because the observation period was short, future studies should investigate the survival rate in patients taking SEC compared with that of patients taking UST. In 20% of patients treated with IFX, more side-effects, mainly infusion reactions, was observed compared with other biologics.[15]

In 8.1% of patients, biologic use was terminated because of unrelated comorbidities, namely gastric cancer, bone marrow transplantation scheduled for blood disorders, pregnancy, onset of dementia and liver dysfunction. A large proportion of psoriatic patients are middle-aged or older, and therefore incidental association of such conditions is common. Biologic administration was terminated in only two patients because of malignancy. There is no clear evidence that biologic products will cause growth in malignant tumors.[16,17,25] Another patient had colon cancer, but restarted biologics 1.5

years after surgery because of a severe exacerbation of psoriasis. The patient has been followed without recurrence of colon cancer. Pregnancy is also a possible event for patients who undergo biologic treatment, although only one such occasion was found in our survey. In the guidelines, it is ideal that anti-TNF agents are stopped before pregnancy and resumed after delivery.[25–28] Immunoglobulin G is actively transferred into fetal serum through the placenta, but this begins in the third trimester of pregnancy. Therefore, the use of biologics is generally accepted as beneficial during the first two trimesters of pregnancy.[29] .Additionally, biologic treatment is considered to be safe during breast-feeding. Future research should focus on determining which drug to use, and when to stop taking the drug in case of pregnancy.

Economic burden caused 8.1% of patients to stop taking biologics (Fig. 5b). In the Japanese health insurance system, the patients are required to pay a co-payment (30% of total cost), and younger patients have a relatively heavier burden. Some young patients cannot continue taking biologics as a treatment because of economic reasons.

Two patients (0.95%) with remission stopped biologic treatment. These patients did not return to the hospital during the research period, and therefore we could not determine whether they remained in remission. Biologics are effective treatments for symptoms in patients with psoriasis and they often improve the patients' quality of life dramatically, but there have been few reports that biologics can cure psoriasis.

Reason for bio-switching

The reason for switching from the first biologic in 64 patients was mainly secondary loss of efficacy or primary ineffectiveness, and these two conditions accounted for more than 80% of changes in treatment. Only 14% of the changes were because of side-effects. Even if the effectiveness of the biologic decreases, bio-switching is not always necessary because effectiveness is often regained by increasing the dose.[13] However, efficacy is often lost again in patients after dose escalation. There is no consensus on whether a biologic should be switched or if the dose should be increased. One reason for the secondary loss of efficacy is antidrug antibodies.[13] It has been reported for SEC that antidrug antibodies are rarely found,[30] but our study revealed that 41% of patients taking SEC discontinued this treatment because of secondary loss of efficacy. This observation

indicates that antidrug antibodies may not be the only determining factor in secondary failure, but also a high loading dose may matter. All biologics have a high loading dose at the beginning of treatment, but IFX, SEC and IXE have very high loading doses, whereas ADA and BRO have modest loading doses. The secondary loss of efficacy may be because of the lower dose after finishing the loading dose in some drugs. For a more precise prediction of secondary failure, patient and drug factors should be thoroughly analyzed in a study with a larger sample size.

For PsA, TNFi was administrated to over half the patients, although this proportion was decreasing. TNFi are generally recommended for peripheral arthritis;[31] however, our survey revealed that the overall survival rates of TNFi were not different from that of other drugs. This may be because the patients' background was not randomly adjusted. We observed that some patients were changed from TNFi to SEC with a satisfactory effect as previously reported.[18] .There is currently no consensus on the first-line treatment for patients with PsA, and further study is required.

Limitations

There were some limitations to this study. This was a survey of a single institute and there were a relatively small number of patients. Newer drugs have a shorter marketing period than older drugs, so survival of patients taking each drug was difficult to assess. This was a retrospective study and switching of biologics is not always dependent on an objective index such as Psoriasis Area Severity Index or Dermatology Life Quality Index, but rather it is dependent on the patient's request or physician's decision. A larger multicenter study is needed to determine the optimal treatment for psoriasis and psoriatic arthritis patients. In the future, more drugs will be introduced into the market. The usefulness of all drugs needs to be evaluated through detailed observation on a larger scale.

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Conflict of Interest

None declared.

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Table 1. Patients' background

	Male	**Female**	**Total**	***p*-value**
n	158	53	211	
Age, years	49+-14	53+-17	50+-15	
Onset age, years	39+-16	44+-21	40+-17	
BMI	25+-4	23+-5	24+-4	
Family history				
Psoriasis vulgaris	16 (10.1%)	9 (16.9%)	25 (11.8%)	*0.2189*
Atopic dermatitis	5 (3.2%)	2 (3.8%)	7 (3.3%)	*1.00*
Life history				
Smoking	80 (50.6%)	14 (26.4%)	94 (44.5%)	*0.0024***
Drinking	61 (38.6%)	15 (28.3%)	76 (36%)	*0.1902*
Medical history				
Tonsillitis	12 (7.6%)	2 (3.8%)	14 (6.6%)	*0.5254*
Cerebral infarction	3 (1.9%)	2 (3.8%)	5 (2.4%)	*0.6014*
Myocardial infarction	4 (2.5%)	1 (1.9%)	5 (2.4%)	*1.00*
Disease type				
Psoriatic arthritis	42 (26.6%)	18 (34%)	60 (28.4%)	*0.3789*
Pustular psoriasis	7 (4.4%)	6 (11.3%)	13 (6.2%)	*0.0958*
Guttate psoriasis	0 (0%)	2 (3.8%)	2 (0.9%)	*0.0622*
Erythroderma	3 (1.9%)	0 (0%)	3 (1.4%)	*0.5741*
Severity of skin symptom				
Severe	61 (38.6%)	13 (24.5%)	74 (35.0%)	*0.0690*
Moderate	60 (38%)	26 (49.1%)	86 (40.8%)	*0.1961*
Mild	37 (23.4%)	14 (26.4%)	51 (24.2%)	*0.8539*
BSA				
≧10%	87 (55.1%)	22 (41.6%)	109 (51.7%)	*0.1120*
<10%, ≧5%	37 (23.4%)	11 (20.7%)	48 (22.7%)	*0.8500*
<5%	34 (21.5%)	20 (37.7%)	54 (25.6%)	*0.0282**
Nail symptom	68 (43%)	20 (37.7%)	88 (41.7)	*0.5239*
Itching	66 (41.8%)	27 (51%)	93 (44.1%)	*0.2659*
Comorbidities				
Obesity	45 (28.5%)	16 (30.2%)	62 (29.4%)	*0.8619*
Diabetes	29 (18.3%)	9 (17%)	38 (18.1%)	*1.00*
Hypertension	52 (32.9%)	21 (39.6%)	73 (34.6%)	*0.4062*

Hyperlipidemia	40 (25.3%)	16 (30.2%)	56 (26.5%)	*0.4784*
Hyperuricemia	23 (14.5%)	3 (5.7%)	26 (12.3%)	*0.0969*

Statistically significant differences between sexes are shown as *P < 0.05 and **P < 0.01.
BMI, body mass index; BSA, body surface area.

Table 2. Frequency of use for each biologic in patients with psoriasis vulgaris (PsV) or psoriatic arthritis (PsA) calculated by patient-year

Biologics	Total	no PsA	PsA	*p-value*
Infliximab	142	108	34	*0.0002*****
Adalimumab	222	183	39	*0.0467**
Ustekinumab	223	210	13	*0.0001*****
Secukinumab	110	104	6	*0.0061*****
Ixekizumab	12	12	0	*0.3867*
Brodalumab	33	24	9	*0.0328**

Statistically significant differences between psoriasis vulgaris/psoriatic arthritis (PsV/PsA) groups are shown as *P < 0.05 and **P < 0.01.

Table 3. Demographic characteristics of continuously used/switched drugs in psoriasis vulgaris patients

	IFX	ADA	UST	SEC	IXE	BRO	Total
n	48	71	58	25	2	7	211
Male:Female (% male)	37/11(77.1%)	50/21 (70.4%)	44/14 (75.9%)	20/5 (80%)	2/0 (100%)	5/2 (71.4%)	158/53
Age(years)±SD	47±13	50±13	50±17	53±17	55±12	65±14	50±15
Onset age (years)±SD	35±15	40±15	41±19	44±21	51±16	45±16	40±17
BMI (kg/m²)	24±3	25±5	24±3	24±5	21±3	27±7	24±4
PASI (severe/moderate/mild patients)	17/12/11	19/21/12	16/16/13	6/5/5	1/0/0	1/3/0	60/54/41
PsV/PsA	33/10	31/12	54/4	24/1	2/0	7/0	151/27
Patients treated with a single drug	19	46	50	24	2	6	147 (69.7%)
Switched patients	29 (13.7%)	25 (11.8%)	8 (3.8%)	1 (0.5%)	0 (0%)	1 (0.5%)	64 (30.3%)
Duration of first biological treatment (median, range months)	35 (1-229)	18 (1-233)	41 (179-2)	34 (80-3)	10 (6-14)	5 (1-32)	26 (1-229)
Second-line drug (number)							
IFX	-	4	0	0	0	0	4
ADA	10	-	3	0	0	0	13
UST	9	15	-	0	0	0	24
SEC	8	4	3	-	0	0	15
IXE	0	0	1	0	-	1	2
BRO	4	2	1	1	0	-	8
Duration of first biological treatment (median, range months)	60 (1-112)	15 (3-153)	26 (2-133)	33 (5-78)	15 (14-15)	7 (3-34)	20 (1-153)

ADA, adalimumab; BMI, body mass index; BRO, brodalumab; IFX, infliximab; IXE, ixekizumab; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; PsV, Psoriasis vulgaris; SD, standard deviation; SEC, secukinumab; UST, ustekinumab.

Table 4. Reasons for discontinuation, termination and switching for each drug in patients with psoriasis vulgaris

Reasons	All discontinued						Terminated					Switched				
	IFX	ADA	UST	SEC	IXE	BRO	IFX	ADA	UST	SEC	BRO	IFX	ADA	UST	SEC	BRO
Primarily ineffectiveness for skin symptom	9	22	19	3	1	1	-	5	2	-	1	7	8	5	-	-
Secondary loss of efficacy for skin symptom	18	23	16	13	-	6	-	5	2	2	-	15	12	3	1	1
Side effect	9	4	1	1	1	-	-	-	1	-	-	6	3	-	-	-
Problem on self-injection	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
Economic problem	-	3	2	-	-	-	-	2	2	1	-	-	1	-	-	-
Patients' preference/Quit visiting	7	17	8	14	-	1	1	10	2	3	-	1	-	-	-	-
Comorbidities	2	3	1	1	-	-	2	2	1	-	-	-	1	-	-	-
Remission	1	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-
Referral to nearby hospitals	-	-	-	-	-	-	3	7	3	2	1	-	-	-	-	-

ADA, adalimumab; BRO, brodalumab; IFX, Infliximab; IXE, ixekizumab; SEC, secukinumab; UST, ustekinumab.

Fig. 1

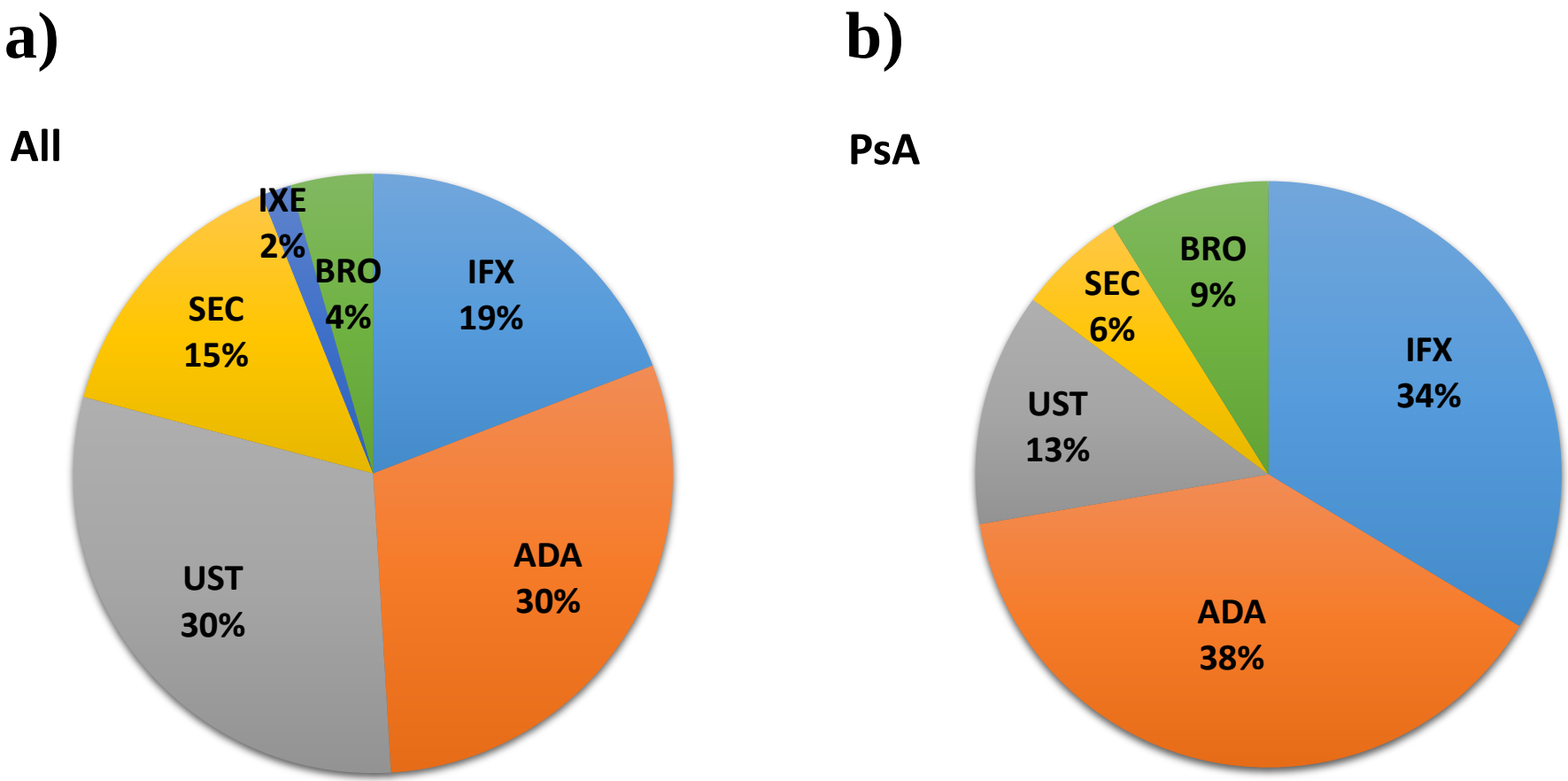

a)
All
IXE
2%
BRO
4%
IFX
19%
SEC
15%
ADA
30%
UST
30%
b)
PsA
BRO
9%
SEC
6%
IFX
34%
UST
13%
ADA
38%

Fig. 2

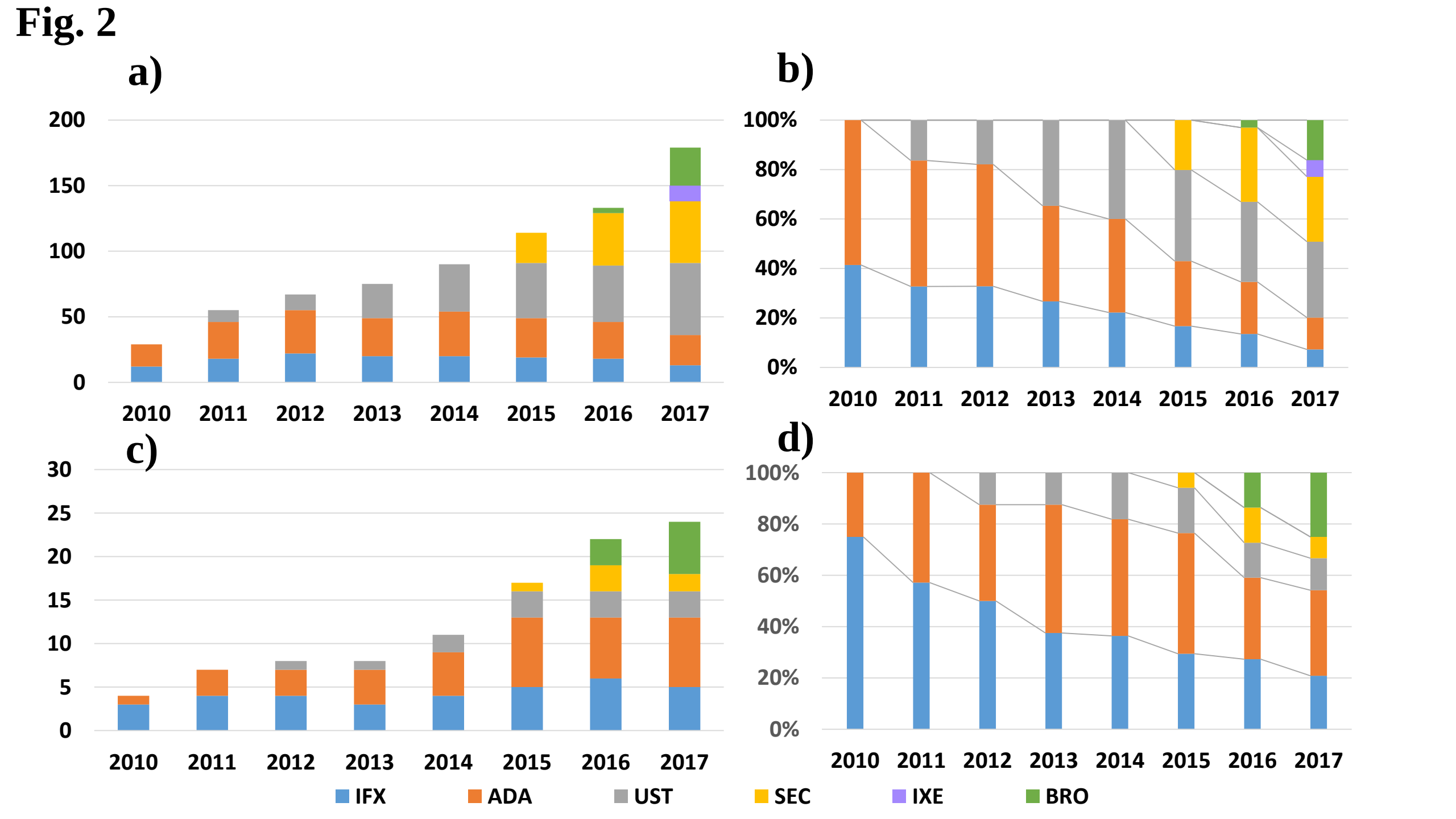

a)
200
150
100
50
0
2010
2011
2012
2013
2014
2015
2016
2017
b)
100%
80%
60%
40%
20%
0%
2010
2011
2012
2013
2014
2015
2016
2017
c)
30
25
20
15
10
5
0
2010
2011
2012
2013
2014
2015
2016
2017
d)
100%
80%
60%
40%
20%
0%
2010
2011
2012
2013
2014
2015
2016
2017
IFX
ADA
UST
SEC
IXE
BRO

Fig. 3

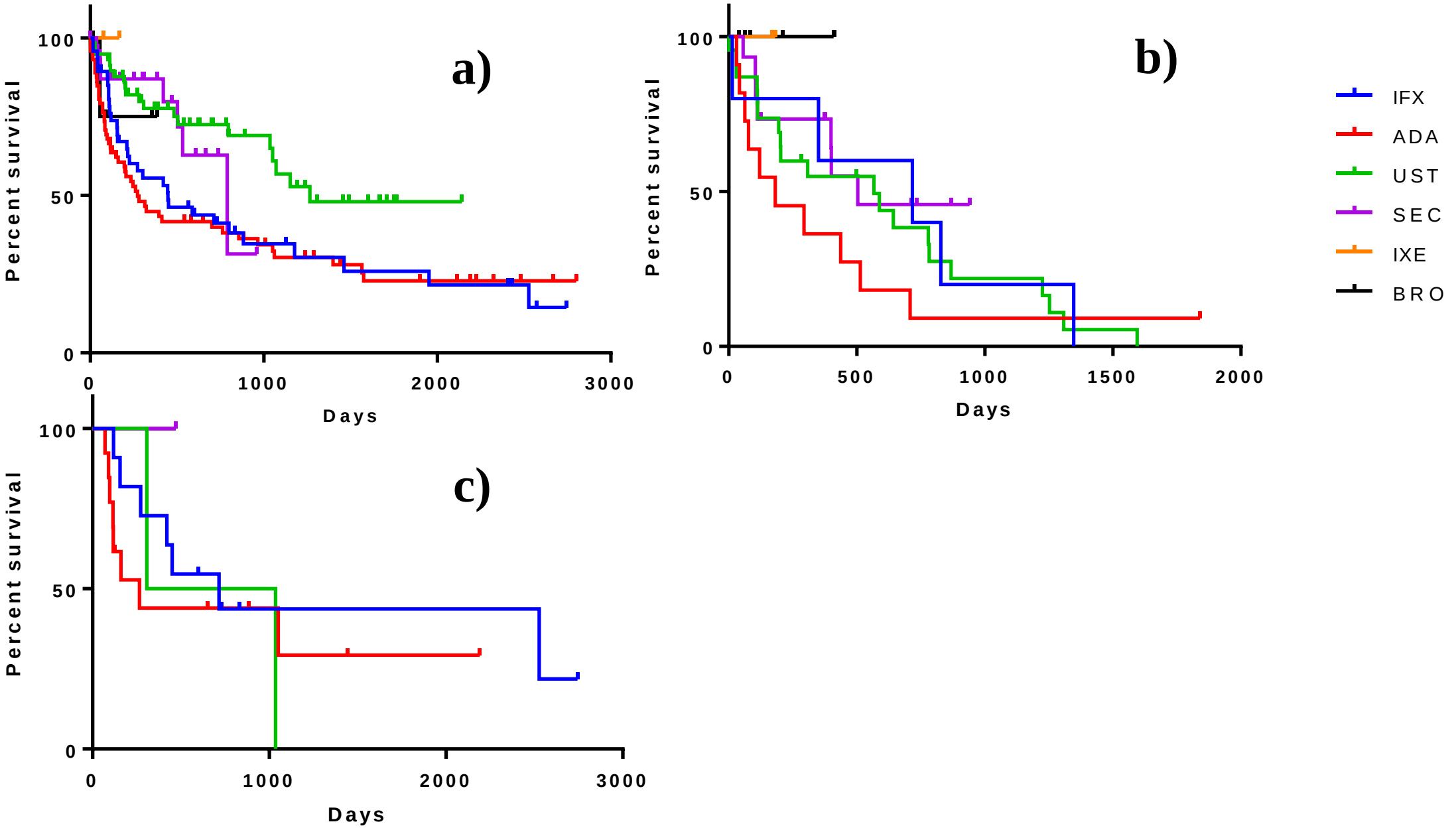

a)
b)
c)
Percent survival
Days
100
50
0
0
1000
2000
3000
500
1500
IFX
ADA
UST
SEC
IXE
BRO

Fig. 4

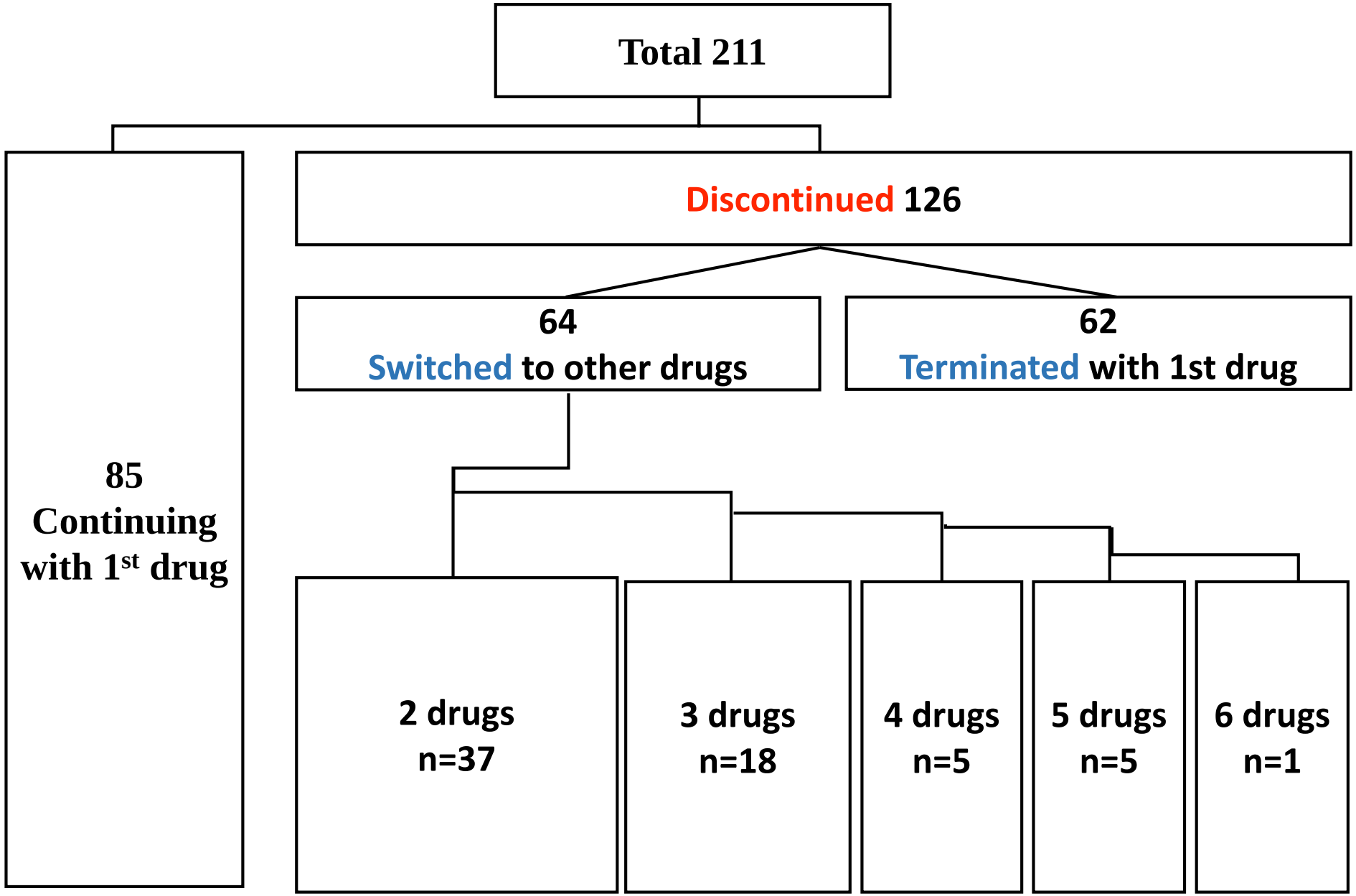

Total 211
85
Continuing
with 1st drug
Discontinued 126
64
Switched to other drugs
62
Terminated with 1st drug
2 drugs
n=37
3 drugs
n=18
4 drugs
n=5
5 drugs
n=5
6 drugs
n=1

Fig. 5

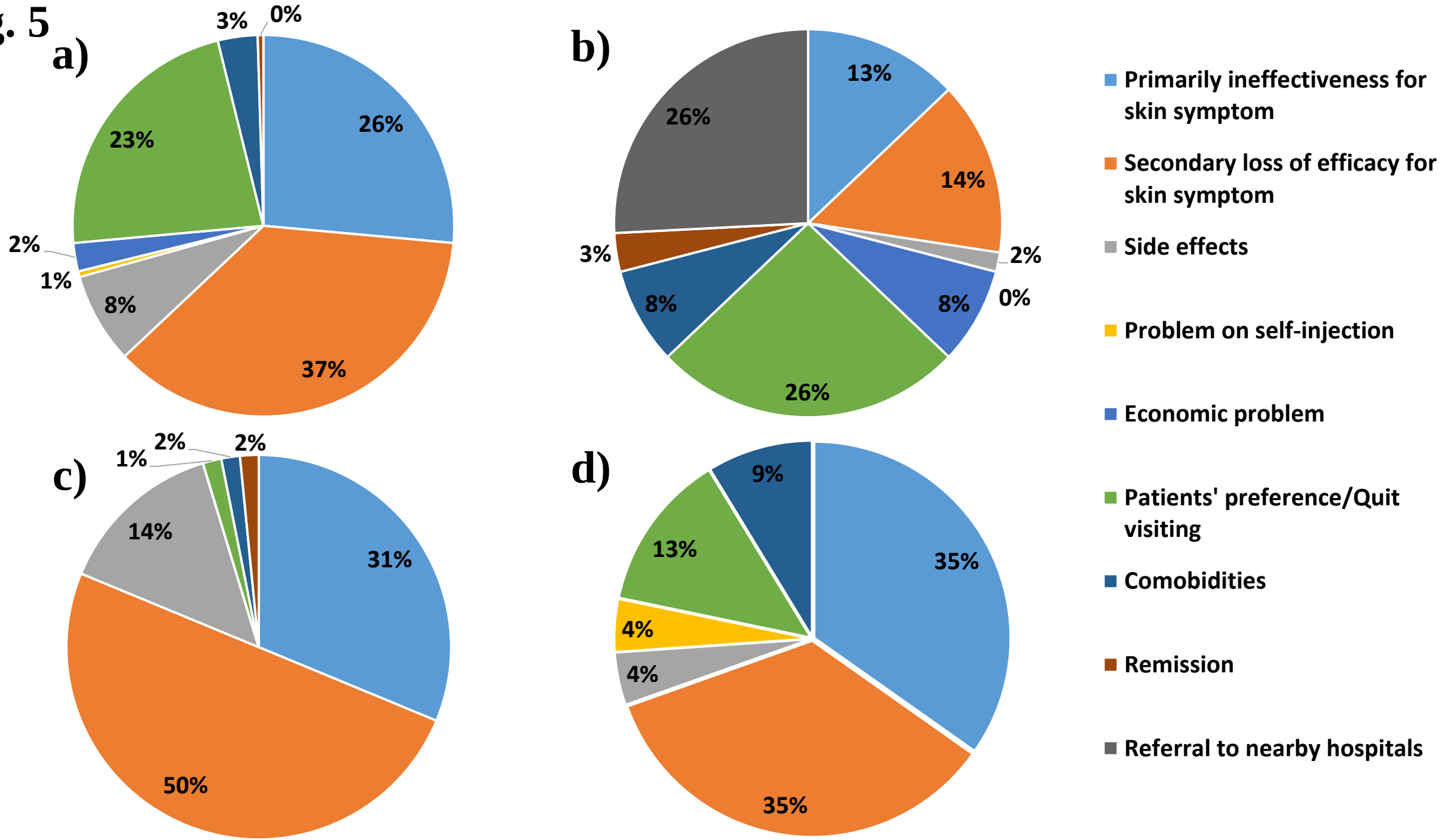

a)
26%
37%
8%
1%
2%
23%
3%
0%
b)
13%
14%
2%
0%
8%
26%
8%
3%
26%
c)
31%
50%
14%
1%
2%
2%
d)
35%
35%
4%
4%
13%
9%
Primarily ineffectiveness for skin symptom
Secondary loss of efficacy for skin symptom
Side effects
Problem on self-injection
Economic problem
Patients' preference/Quit visiting
Comobidities
Remission
Referral to nearby hospitals

Fig. S1

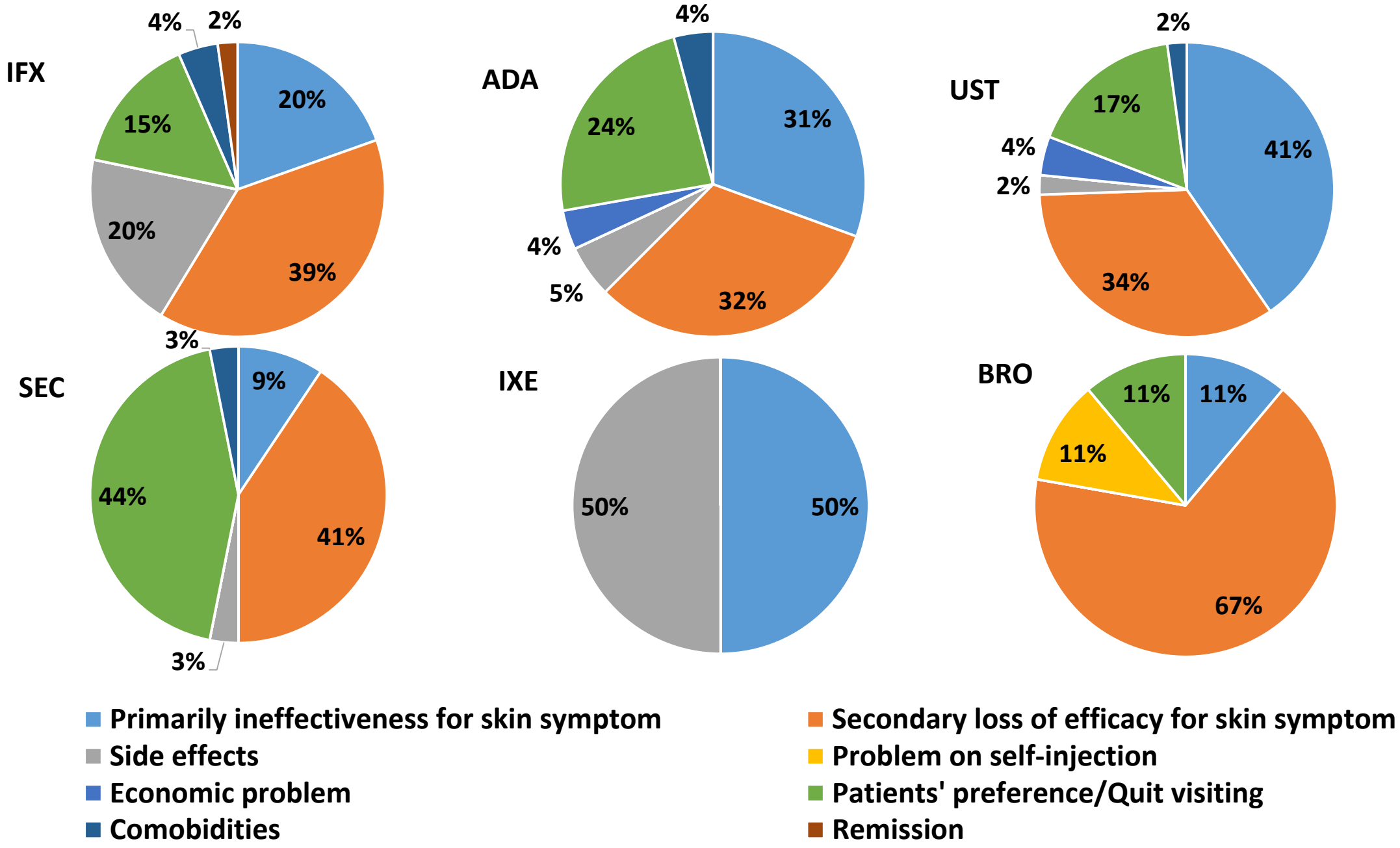
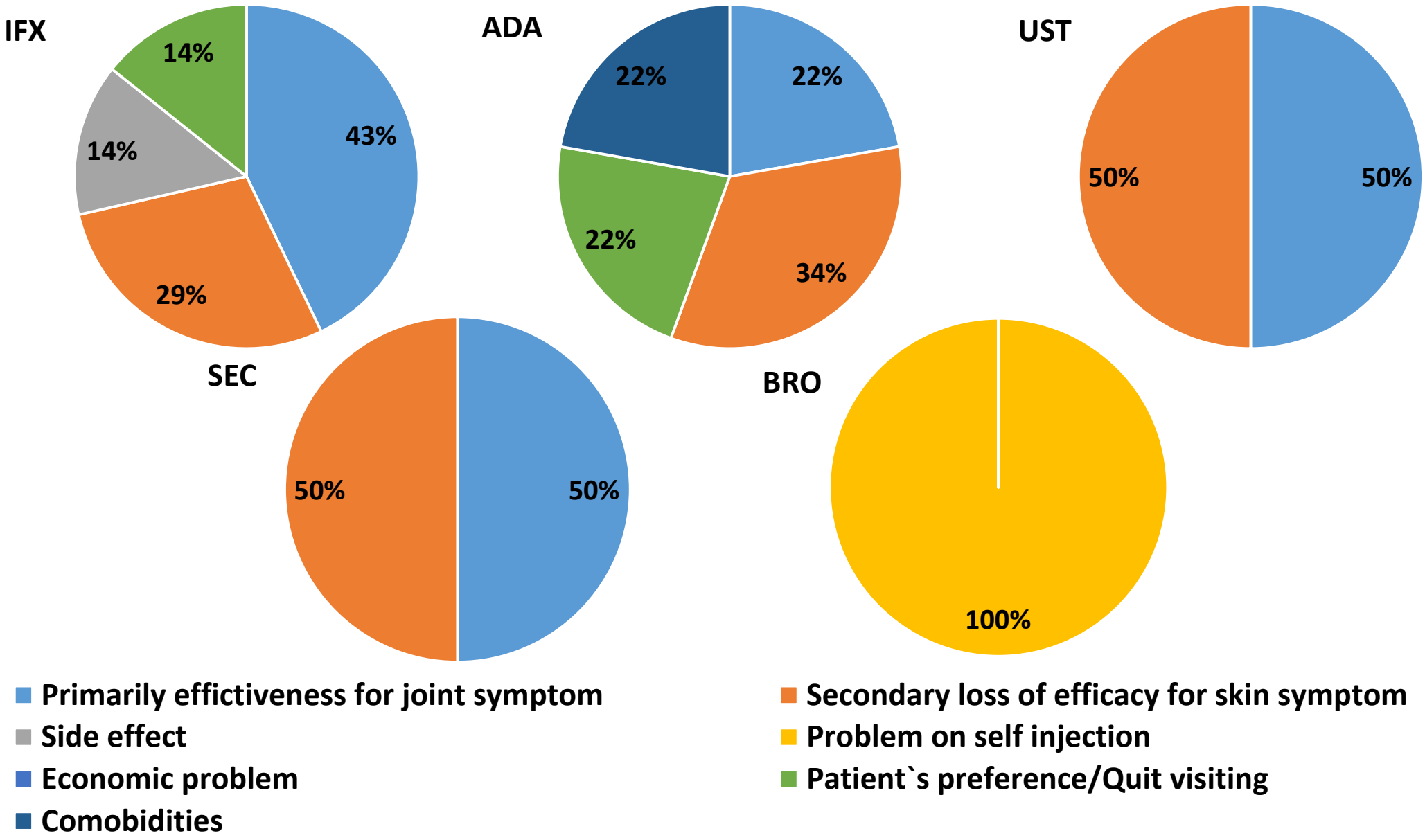

IFX
20%
39%
20%
15%
4%
2%
ADA
31%
32%
5%
4%
24%
4%
UST
41%
34%
2%
4%
17%
2%
SEC
9%
41%
3%
44%
3%
IXE
50%
50%
BRO
11%
67%
11%
11%
Primarily ineffectiveness for skin symptom
Secondary loss of efficacy for skin symptom
Side effects
Problem on self-injection
Economic problem
Patients' preference/Quit visiting
Comobidities
Remission

Fig. S2


IFX
14%
43%
14%
29%
ADA
22%
22%
22%
34%
UST
50%
50%
SEC
50%
50%
BRO
100%
Primarily effictiveness for joint symptom
Side effect
Economic problem
Comobidities
Secondary loss of efficacy for skin symptom
Problem on self injection
Patient`s preference/Quit visiting