A Cross-sectional Survey on the Preference of Patients with Rheumatoid Arthritis for Route of Administration of Disease-Modifying Anti-Rheumatic Drugs: Oral Target-Specific Versus Parenteral Biologic

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ABSTRACT: **Background:** Guidelines recommend initiation of parenteral biologic or oral target-specific disease-modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) in rheumatoid arthritis (RA) patients who do not adequately respond to conventional DMARDs.
Objectives: To compare the preferred route of administration of bDMARDs or tsDMARDs in RA patients who were previously treated with at least one type.
Methods: A cross-sectional survey was conducted of consecutive RA patients previously prescribed bDMARDs or tsDMARDs. We analyzed the factors associated with patients' preferred route of administration.
Results: The cohort included 95 patients, mostly female (72.6%), seropositive (81.05%), mean age 63.4 ± 11.9 years. The oral route was preferred by 39 patients (41%) and 56 (59%) preferred the parenteral route. Most patients (65.9%) preferred to continue with their current route ($P < 0.001$). Switching from a current route was less common with patients who were currently using the oral route (13.3% vs. 38.2%, $P = 0.04$). Many patients (53.8%) who preferred the oral route had never experienced it before, while this was rare (3.6%) regarding the parenteral route ($P = 0.0001$). Employment status was associated with preference of the subcutaneous route over the intravenous route of bDMARDs ($P = 0.01$). Of the 21 patients who had previously experienced both parenteral and oral treatment, 16 (76.2%) preferred the oral route.
Conclusions: RA patients preferred to continue treatment with an administration route they have already experienced. However, when choosing an unexperienced route, significantly more patients preferred the oral route. Our results strengthen the understanding of patient preferences, which could improve drug adherence, compliance, and disease outcome.

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KEY WORDS: disease-modifying anti-rheumatic drugs (DMARDs), patient preference, rheumatoid arthritis (RA), route of administration, tofacitinib

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammatory erosive polyarthritis. Most patients test positive for rheumatoid factor (RF) and/or anti-citrullinated peptide antibody (ACPA) [1]. The goal of treating RA is disease remission or a state of low disease activity (LDA), as assessed by recognized numerical scales [2,3]. The European League Against Rheumatism (EULAR) [4] and the American College of Rheumatology (ACR) [5] recommend that patients who do not adequately respond to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs such as methotrexate) should be treated with a biologic DMARD (bDMARD) or a target-specific DMARD (tsDMARD) [4,5] to achieve disease remission or LDA . Biologic or target-specific therapies have been shown to be highly effective in treating RA. They ameliorate joint signs and symptoms [6,7] and halt progression of structural damage and physical disability [4,8], with a commensurate decrease in cost of care [7]. They have also been associated with better quality-adjusted life-years than csDMARDs [8].

The bDMARDs can be administered intravenously (IV) at an infusion center or subcutaneously by self-injection at home. Some are available for use by both routes. The first approved tsDMARD was tofacitinib, a pan-Janus Kinase (JAK) inhibitor [9]. Tofacitinib is administered orally, twice daily, and like bDMARDs, is indicated for the treatment of patients with active RA who did not respond completely to csDMARDs [1]. Both the bDMARDs and the tsDMARDs may be given together with methotrexate or as monotherapy. Although they have not been strictly evaluated in head-to-head trials, they are considered to be equally efficacious [10]. A recent study showed that tofacitinib median drug survival (the median time a patient uses a drug until stopping it for various reasons) was 5 years, similar to other bDMARDS [11]. These findings leave the decision of which drug to use to the discretion of the physician. The relative importance of treatment attributes has barely been investigated in RA since the addition of oral medications such as the tsDMARDs to the list of available therapies. The route of

administration may be a major differentiator among the drugs, especially if the patient's preference might influence adherence and disease outcome.

One study conducted across European countries showed that rheumatologists avoided selecting a treatment that the patient disliked [12]. Patient preference of route of administration has been investigated for other treatments such as chemotherapy [13], endocrine drugs [14], antimicrobials [15], and pain drugs [16]. The results often showed that when efficacy was not altered, patients tended to prefer oral therapy [13,14]. A study of patients undergoing intravenous (IV) or subcutaneous treatment with bDMARDs found that the majority, when given a choice, opted to continue with the route they were currently using [17]. A meta-analysis found subcutaneously administered therapy was often, but not always, preferred over IV therapy [18]. However, at the time of these investigations, oral tsDMARDs were not widely available. In a later study specifically addressing tsDMARDs, the majority of patients (56.4%) expressed a preference for the oral route over the other routes [19].

The purpose of this present study was to compare patient preference between the parenteral route of administration (subcutaneously or IV bDMARDs) and the relatively new available oral route of administration (tsDMARD).

PATIENTS AND METHODS

PATIENTS

The study was conducted at Rabin Medical Center, a major tertiary, university-affiliated, hospital. The 1995 National Health Insurance Act stipulates that all Israeli residents are entitled to publicly funded health insurance, which covers a comprehensive and uniform "basket" of healthcare services that is updated once a year. Due to this system, all bDMARDs and tsDMARDs have the same patient co-payment. For purposes of the present study, we conducted a cross-sectional survey of consecutive patients who fulfilled the ACR criteria for RA [20] and were under routine follow-up and treatment at the rheumatology outpatient clinic of Rabin Medical Center between March 2017 and January 2018. The study cohort included only patients who were previously treated with at least one bDMARD or tsDMARD. Patients unable or unwilling to answer the survey questions were excluded as were patients with an additional autoimmune or autoinflammatory rheumatic disease, except for secondary Sjogren's syndrome and osteoarthritis. All patients who signed an informed consent completed the survey. The survey was administered and completed in Hebrew (help from an independent translator was permitted). The study was approved by our institutional ethics committee.

STUDY QUESTIONNAIRE

Questions on patient background were divided into categories.

- Demographics and social data: age, sex, employment status, marital status, and smoking
- RA features at the time of the study such as: disease duration, seropositivity (RF and/or ACPA); and RA medications used (for at least 3 consecutive months) as well as at the time of the survey, including csDMARDs, bDMARDs, and tsDMARDs

We systematically searched and reviewed the Clalit Health Services electronic database at the time of the survey to determine the following co-morbidities: past or present cardiovascular disease, diabetes mellitus, hypertension, chronic kidney disease, chronic lung disease, history of joint replacement surgery, and history of solid or hematological malignancy. In addition to the background questions, patients were asked three questions pertaining to their preferred route of administration of bDMARDs or tsDMARDs.

- If the choice of the drug is based solely on personal considerations, and assuming no differences in efficacy, would you prefer that the drug be administered by intravenous infusion at the outpatient infusion center at the hospital or subcutaneous injection at the patient's place of living, or a twice daily oral drug?
- If the choice of the parenteral drug is based solely on personal considerations, and assuming no differences in efficacy, would you prefer that the drug be administered intravenously at the outpatient infusion center in the hospital or twice daily orally?
- If the choice of the drug is based solely on personal considerations, and assuming no differences in efficacy, would you prefer that the drug be administered by subcutaneous injection at home or twice daily oral drug?

MEDICAL DATA

We systematically evaluated the Clalit Health Services electronic database of each patient for RA features and DMARDs that were prescribed and drawn from the pharmacy by the patient for at least 3 months. To assess disease status at the time of the survey, erythrocyte sedimentation rate (ESR), and serum high-sensitive C-reactive protein (hsCRP) levels were assayed. In addition, the treating physician completed several composite measures of disease. The Disease Activity Score-28 (DAS28), which evaluates the number of tender and swollen joints (out of 28) along with the erythrocyte sedimentation rate (DAS28-ESR) or CRP (DAS28-CRP) measurements on the day the questionnaire was completed, the patient global assessment [7], the Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) [7,8]. Findings were analyzed in relation to demographic and social data, previous experience with bDMARDs, and disease activity at the time of the survey, as well as the presence of co-morbidities.

STATISTICAL ANALYSIS

Data are expressed as mean and standard deviation (SD), median and interquartile range (IQR), or number and per-

centage. We compared patients with RA according to their preferred route of administration (subcutaneous, intravenous, or oral) of bDMARDs or tsDMARDs using *t*-test, Chi-square test, and non-parametric tests, as appropriate. We then evaluated the patient preferences according to their previous and current treatment with bDMARDs or tsDMARDs. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

STUDY COHORT

A total of 96 consecutive patients (72.6% female) met the inclusion criteria. One patient failed to complete the survey and was excluded from the final analysis. Table 1 shows the demographic parameters and co-morbidities of the cohort. The mean age of the cohort was 63.4 ± 11.9 years (range 35–86) at the time of the study and 47.7 ± 14.4 years (range 13–75) at diagnosis. The mean duration of RA was 14.9 ± 9.2 years (range 2–37 years). Seropositivity for RF and/or ACPA was documented in 77 patients (81.05%).

Table 1. Epidemiological data and co-morbidities in 95 patients with rheumatoid arthritis

Variable	Value (n=95)
Demographics	
Age in years, mean ± SD	63.4 ± 11.9
Age in years at RA diagnosis	47.7 ± 14.4
Female	69 (72.6%)
Education in years, median ± IQR	12.5 ± 4.2
Never smoked	58 (61.1%)
Current smoker	7 (7.4%)
Previous smoker	26 (27.4%)
Living with other family members	82 (86.3%)
Employed	36 (37.9%)
Co-morbidity	
Cardiovascular disease	12 (12.6%)
Myocardial infarction	7 (7.4%)
Stroke	8 (8.4%)
Chronic lung disease	8 (8.4%)
Diabetes mellitus	15 (15.8%)
Hypertension	34 (35.8%)
Congestive heart failure	5 (5.3%)
Chronic kidney disease ≤ stage 3	2 (2.1%)
Malignancy	5 (5.3%)
Joint replacement	15 (15.8%)
Osteoporosis	39 (41.1%)
Bone fracture	19 (20%)

Values are presented as n (%), unless otherwise stated
IQR = interquartile range, RA = rheumatoid arthritis, SD = Standard deviation

PATIENT PREFERENCES

In response to the first question pertaining to the preferred route of administration of bDMARDs/tsDMARDs, 39 patients (41%) preferred the oral route and 56 (59%) preferred the parenteral route (subcutaneously or intravenously) [Table 2]. Within the parenteral group, 15 patients (15.8%) preferred the IV route and 41 (43.2%) preferred subcutaneously. In response to the second and third questions, when given the options of the IV or daily oral route, 33 patients (34.7%) preferred the IV route and 62 (65.3%), the oral route. When given the options of the subcutaneous or daily oral route, 40 patients (42.1%) preferred the subcutaneous route and 55 (57.9%), the oral route. The patients' preferred route of administration of bDMARDs/tsDMARDs was not associated with age, sex, level of education, seropositivity for RF and/or ACPA, disease activity scores at the time of the survey, or current use of csDMARDs such as methotrexate. There was a significant association of employment status with patient preference of the subcutaneous route over the IV route of bDMARDs ($P = 0.01$), but not over the oral route of tsDMARDs.

PREVIOUS EXPERIENCE

The bDMARDs administered (previously or currently) included tumor necrosis factor-α inhibitors (adalimumab, infliximab, etanercept, certolizumab, golimumab) (n=82), a B-cell depletion drug (rituximab) (n=31), an anti-interleukin (IL)-6 receptor antibody (tocilizumab) (n=23), and a T-cell co-stimulation blocker (abatacept) (n=22). The oral tsDMARD administered was tofacitinib (n=23). At the time of the survey 62 patients (65.3%) had been treated with more than one bDMARD or a tsDMARD, with a median of 2 (IQR 1–3) bDMARDs/tsDMARDs. IV administration of a biologic drug had been experienced (present or past) by 52 patients (54.7%), subcutaneous administration of a biologic drug by 82 patients (86.3%), and oral administration of tofacitinib by 23 patients (24.2%). Both parenteral and oral administration were prescribed to 21 patients (22.1%) with 8 patients using the oral and subcutaneous routes, 2 the IV and oral routes, and 11 all three routes. Previous experience was shown to correlate with the preferred route of administration since 14 of the 15 patients (93.3%) who selected IV treatment ($P < 0.001$), 40 of the 41 patients (97.6%) who selected subcutaneous treatment ($P = 0.006$), and 18 of 39 patients (46.2%) who selected oral treatment ($P = 0.001$) previously experienced their preferred route. While only 2 of the 56 (3.6%) patients who preferred the parenteral route of administration of bDMARDs had never experienced it (one subcutaneous and one IV) 21 of the 39 patients (53.8%) who preferred the oral route of tsDMARDs had never experienced it ($P = 0.0001$). Of the 21 patients who had experienced both

the parenteral and oral routes of administration, 16 patients (76.2%) preferred the oral route and only 5 (23.8%), the parenteral route (n=5, SC, n=0, IV).

CURRENT EXPERIENCE

Current experience was associated with the preferred route of administration. For 34 of the 52 patients (65.4%) treated via the subcutaneous route ($P < 0.001$), 13 of the 24 patients (54.2%) treated by the IV route ($P < 0.001$), and 13 of the 15 patients (86.7%) treated with the oral route ($P < 0.001$), their current route was the one they preferred. Only 2 patients (13.3%) who were currently treated via the oral route preferred not to continue with it as opposed to 29 of the 76 patients (38.2%) currently treated via a parenteral route ($P = 0.04$).

DISCUSSION

The principle finding of our cross-sectional survey was that patients previously treated with bDMARDs or tsDMARD tended to prefer the route of administration they were already familiar with. This experience was the main factor affecting their current choice. The patients appeared to find the daily oral route of tsDMARDs more advantageous. Many patients preferred the oral route even when they had no experience with it, which was not the case for the parenteral route (IV or subcutaneous). The tendency to adhere to the current route of treatment was significantly higher in patients receiving oral tsDMARD treatment than in patients receiving bDMARD parenteral treatment. Moreover, 76.2% of the patients who had experienced all three routes preferred the oral one. The increasing number of treatment options for RA poses a complex decision-making issue for physicians in terms of how and when each medication should be initiated. The various bDMARDs, as well as the tsDMARD, are all considered to have equal efficacy [10]. Therefore, individualized treatment strategies need to be used so patients can participate in the decision-making process [21,22].

By taking patient needs and preferences into account, clinicians can improve adherence to therapy with consequent improvement in disease control and overall outcome [23]. A previous survey showed that rheumatologists were even willing to trade efficacy for patient satisfaction if disease activity was moderate [24]. Our findings concur with previous studies suggesting a tendency of patients with [25] and without [13-16] RA to opt for oral therapy. However, most of the studies that included patients with RA grouped csDMARDs and bDMARDs together and did not account for such confounders as cost and efficacy differences. Moreover, since the availability of the bDMARDs to treat RA patients, most studies were performed before the tsDMARDs era and therefore could not assess the preference of oral route in these modern treatments [25]. One study investigated tsDMARDs specifically and found that the majority of patients (56.4%) preferred the oral route [17].

Table 2. Comparison of patients with rheumatoid arthritis by their preferred route of administration of biologic or oral target-specific disease-modifying anti-rheumatic drugs

Variable	Intravenous (n=15)	Subcutaneous (n=41)	Oral (n=39)	*P* value
Demographics				
Age in years, mean	64.6 (13.4)	63.4 (12.8)	62.9 (10.6)	0.51
Female	10 (66.6)	28 (68.3)	31 (79.4)	0.45
Living with other family members	13 (86.6)	35 (85.3)	33 (84.6)	0.93
Never smoked	11 (73.3)	27 (65.8)	20 (51.2)	0.09
Current smoker	2 (13.3)	13 (31.7)	18 (46.1)	0.09
Education in years, median (IQR)	12.0 (10.0–14.0)	12.0 (10.0–15.5)	12.0 (12.0–16.0)	0.79
Academic education	5 (33.3)	16 (39.0)	14 (35.8)	0.91
Distance of home from infusion center (km), median (IQR)	9.0 (3.0–15.0)	9.2 (3.1–25.0)	8.7 (4.0–26.0)	0.74
Currently employed	2 (13.3)	21 (51.2)	13 (33.3)	0.01†
Retired due to RA	6 (40.0)	6 (14.6)	12 (30.7)	0.23
Owns a car	8 (53.3)	26 (63.4)	25 (64.1)	0.71
Drives a car	7 (46.6)	25 (60.9)	21 (53.8)	0.52
Needs an escort for follow-up	4 (26.6)	10 (24.4)	8 (20.5)	0.90
Co-morbidity				
Cardiovascular disease	3 (20.0)	4 (9.7)	5 (12.8)	0.59
Myocardial infarction	0 (0.0)	2 (4.8)	5 (12.8)	0.19
Stroke	2 (13.3)	3 (7.3)	3 (7.6)	0.70
Chronic lung disease	1 (6.6)	1 (2.4)	6 (15.3)	0.11
Diabetes mellitus	2 (13.2)	6 (14.6)	7 (17.9)	0.88
Hypertension	8 (53.3)	10 (24.4)	16 (41.0)	0.09
Congestive heart failure	1 (6.6)	2 (4.8)	2 (5.1)	0.96
Chronic kidney disease ≤ stage 3	1 (6.6)	1 (2.4)	0 (0.0)	0.30
Malignancy	1 (6.6)	0 (0.0)	4 (10.2)	0.11
Joint replacement	4 (26.6)	5 (12.1)	6 (15.3)	0.41
Osteoporosis	7 (56.6)	14 (34.1)	18 (46.1)	0.49
Bone fracture	3 (20.0)	7 (17.1)	9 (23.1)	0.79
Disease-related variables				
Seropositive RA	14 (93.3)	31 (75.6)	32 (82.0)	0.31
Duration of RA in years, median (IQR)	17.0 (12.0–26.0)	12.0 (6.5–20.5)	12.0 (8.0–21.0)	0.09
ESR, median (IQR)	10 (5.0–27.5)	12.0 (6.0–30.0)	24.0 (5.0–46.5)	0.18
CRP, median (IQR)	0.20 (0.0–0.35)	0.31 (0.0–0.94)	0.34 (0.13–1.0)	0.15
DAS28-ESR, median (IQR)	3.13 (2.01–3.74)	2.53 (1.74–3.43)	3.27 (2.14–5.22)	0.34
DAS28-CRP, median (IQR)	2.21 (1.35–3.93)	2.10 (1.49–3.18)	2.45 (1.67–3.94)	0.37
CDAI, median (IQR)	4.0 (1.0–16.0)	4.0 (1.0–11.0)	7.0 (3.0–21.0)	0.23
SDAI, median (IQR)	4.21 (2.0–20.05)	5.45 (1.31–11.58)	6.60 (3.12–20.53)	0.37
MTX – current	7 (56.6)	16 (39.0)	19 (48.7)	0.67
MTX dosage, median (IQR)	15.0 (8.7–16.9)	15.0 (8.1–19.4)	16.2 (12.5–20.0)	
Leflunomide current	0 (0.0)	3 (7.3)	1 (2.5)	0.38
Salazopirin current	0 (0.0)	2 (4.8)	2 (5.1)	0.67
Hydroxychloroquine current	2 (13.2)	4 (9.7)	5 (12.8)	0.88
Prednisone current	0 (0.0)	5 (12.1)	7 (17.9)	0.20

*Values are presented as n (%), unless otherwise stated

†Refers to intravenous vs subcutaneous routes

CDAI = clinical disease activity index, CHF = congestive heart failure, CKD = chronic kidney disease, CRP = C-reactive protein level, DAS = disease activity score, ESR = erythrocyte sedimentation rate, IQR = interquartile range, MTX = methotrexate, RA = rheumatoid arthritis, SDAI = simplified disease activity index

In addition, a recent cross-sectional postal survey of patients with RA showed that the route of administration was the most important medication attribute, with highest rates for the oral route. Conjoint simulation results showed that 56.4% of respondents would prefer an oral route of administration [19]. Our study is unique in that we examined the preference of patients with RA who had already undergone bDMARD or tsDMARD treatment, and some had experience with both the oral and parenteral routes. In our cohort, cost of the medication was not an issue because in the Israeli medical system, there is no difference in the patient co-pay for bDMARDs and tsDMARDs. Given the lack of an association shown here between patient route preferences and disease activity scores, we presume that the patients did not opt for one route over another because they believed it was more effective. Moreover, the lack of an association between patient route preferences and either disease activity score (DAS-28, CDAI, and SDAI) or co-morbidities suggests that their preference was not influenced by their experience with other types of medications that were previously prescribed or were currently being used for other indications.

Although preferences were not affected by demographic variables, employment status was associated with a preference for the subcutaneous over the IV route ($P = 0.01$). This finding is probably attributable, as suggested by others, to the long duration of each IV session, sometimes causing lost work days [17]. Employment status had no significant effect when the parenteral routes were compared to the oral route.

LIMITATIONS

This study was limited by the single-center setting and relatively small number of patients. A larger multicenter population would have provided more statistical power, prevented selection bias, and extended the generalizability of our results. Furthermore, this cross-sectional study assessed patients who were already receiving bDMARDs or tsDMARDs, therefore, recall bias could have influenced patient preferences. Since oral medication is taken twice daily while parenteral medication is taken in intervals between once weekly to once every 8 weeks this may influence a patient's decision. To try and overcome this bias we deliberately did not specify this data in the questionnaire and asked patients to regard route of administration only. In addition, because patients were used to taking daily csDMARDs, this may have less of an influence. However, experienced patients who know the differences between the medications may still be biased by this knowledge. Nevertheless, overall, our results indicate that most patients are satisfied with the route of administration of bDMARDs or tsDMARDs they have already used and overcome this bias. Our subgroup analysis of patients treated parenterally and orally could add to this information. We did not have data on patient adherence or efficacy of treatment.

CONCLUSIONS

The present study expands current knowledge on therapeutic preferences of patients with RA in the era of oral tsDMARDs. While there was no significant difference in preferences for the oral or parenteral route as a group, the patients preferred the routes with which they already had previous or current experience. However, when both routes were experienced, or when choosing an unexperienced route, significantly more patients preferred the oral route. This understanding of patient preference has important implications for the role of drug attributes in individualized treatment strategies, patient participation in the decision-making process, and adherence to treatment and might improve drug adherence and compliance as well as improve disease outcome.

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References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016; 388: 2023-38.
2. Prevoo MLL, van't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
3. Aletaha D, Martinez-Avila J, Kvien TK, Smolen JS. Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. *Ann Rheum Dis* 2012; 71: 1190-6.
4. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
5. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016; 68: 1-26.
6. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database *Syst Rev* 2009; (4): CD007848.
7. Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. *J Manag Care Pharm* 2006; 12: 555-69.
8. Iannone F, Lopalco G, Cantarini L, et al. Efficacy and safety of combination therapy for preventing bone damage in rheumatoid arthritis. *Clin Rheumatol* 2016; 35: 19-23.
9. O'Shea JJ, Schwartz DM, Villarino AV, et al. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med* 2015; 66: 311-28.
10. Tvete IF, Natvig B, Gåsemyr J, et al. Comparing effects of biologic agents in treating patients with rheumatoid arthritis: a multiple treatment comparison regression analysis, *PLoS One* 2015; 10: e0137258.
11. Pope J, Keystone E, Jamal S, et al. Persistence of tofacitinib in the treatment of rheumatoid arthritis in open-label, long-term extension studies up to 9.5 Years; A*CR Open Rheumatology* 2019; 1 (2): 73-82.

12. Hifinger M, Hiligsmann M, Ramiro S, et al. Economic considerations and patients' preferences affect treatment selection for patients with rheumatoid arthritis: a discrete choice experiment among European rheumatologists. *Ann Rheum Dis* 2017; 76: 126-32.
13. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997; 15: 110-5.
14. Fallowfield L, Atkins L, Catt S, et al. Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol* 2006; 17: 205-10.
15. Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev* 2001; (4): CD002845.
16. Underwood M, Ashby D, Cross P, et al; TOIB study team. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. *BMJ* 2008; 336: 138-42.
17. Huynh TK, Ostergaard A, Egsmose C, Madsen OR. Preferences of patients and health professionals for route and frequency of administration of biologic agents in the treatment of rheumatoid arthritis. *Patient Prefer Adherence* 2014; 8: 93-9.
18. Durand C, Eldoma M, Marshall DA, Bansback N, Hazlewood GS. Patient preferences for disease-modifying antirheumatic drug treatment in rheumatoid arthritis: a systematic review. *J Rheumatol* 2020; 47 (2): 176-87.
19. Louder AM, Singh A, Saverno K, et al. Patient preferences regarding rheumatoid arthritis therapies: a conjoint analysis. *Am Health Drug Benefits* 2016; 9: 84-93.
20. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
21. Fraenkel L, Fried TR. Individualized medical decision making: necessary, achievable, but not yet attainable. *Arch Intern Med* 2010; 170: 566-9.
22. Fraenkel L, McGraw S. What are the essential elements to enable patient participation in medical decision making? *J Gen Intern Med* 2007; 22: 614-9.
23. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). *Ann Rheum Dis* 2007; 66: 1227-32.
24. Hifinger M, Hiligsmann M, Ramiro S, et al. Influence of disease activity on RA treatment choices in countries with restricted access to expensive, innovative drugs: a discrete choice experiment among rheumatologists. *RMD Open* 2017; 3: e000453.
25. Harrison M, Marra C, Shojania K, Bansback N. Societal preferences for rheumatoid arthritis treatments: evidence from a discrete choice experiment. *Rheumatology* (Oxford) 2015; 54: 1816-25.

Capsule

Active tumor penetration

Anticancer nanoparticle development has relied on the assumption that nanoparticles passively cross leaky blood vessels to enter solid tumors. Using transmission electron microscopy to analyze a glioblastoma xenograft model, **Sindhwani** et al. found that gaps between endothelial cells lining blood vessels are infrequent and do not account for observed nanoparticle accumulation in tumors. Instead, nanoparticles actively enter tumors by transendothelial extravasation. They also show that the vascular architecture in human tumor samples is mostly intact, which supports the observations that nanoparticles enter tumors by means of an active process rather than by a generalized leakiness.

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Capsule

Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy

Synucleinopathies are neurodegenerative diseases that are associated with the misfolding and aggregation of α-synuclein, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Clinically, it is challenging to differentiate Parkinson's disease and multiple system atrophy, especially at the early stages of disease. Aggregates of α-synuclein in distinct synucleinopathies have been proposed to represent different conformational strains of α-synuclein that can self-propagate and spread from cell to cell. Protein misfolding cyclic amplification (PMCA) is a technique that has previously been used to detect α-synuclein aggregates in samples of cerebrospinal fluid with high sensitivity and specificity**. Shahbawaz** and colleagues showed that the α-synuclein-PMCA assay can discriminate between samples of cerebrospinal fluid from patients diagnosed with Parkinson's disease and samples from patients with multiple system atrophy, with an overall sensitivity of 95.4%. The authors used a combination of biochemical, biophysical, and biological methods to analyze the product of α-synuclein-PMCA, and found that the characteristics of the α-synuclein aggregates in the cerebrospinal fluid could be used to readily distinguish between Parkinson's disease and multiple system atrophy. They also found that the properties of aggregates that were amplified from the cerebrospinal fluid were similar to those of aggregates that were amplified from the brain. These findings suggest that α-synuclein aggregates that are associated with Parkinson's disease and multiple system atrophy correspond to different conformational strains of α-synuclein, which can be amplified and detected by α-synuclein-PMCA. The results may help to improve understanding of the mechanism of α-synuclein misfolding and the structures of the aggregates that are implicated in different synucleinopathies, and may also enable the development of a biochemical assay to discriminate between Parkinson's disease and multiple system atrophy.

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