Patient Preference and Adherence

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Antirheumatic Medication Calendar Significantly Improves Adherence in First-Time Methotrexate Users: A Prospective, Single-Blind, Randomized Controlled Trial

Fangfang Yuan[1], Qiong Yang[2], Xin Zhang[1], Jing Luo[1], Jixia Lin[1], Yahui Chen[1], Haiyan Huang[1], Junhong He[2], Luna Cheng[2]

[1]Department of Rheumatology, Immunology, and Orthopedic Medicine, Ningbo No. 6 Hospital, Ningbo, People's Republic of China; [2]Department of Pharmacy, Ningbo No. 6 Hospital, Ningbo, People's Republic of China

Correspondence: Luna Cheng, Department of Pharmacy, Ningbo No. 6 Hospital, 1059 Zhongshan East Road, Yinzhou District, Ningbo City, People's Republic of China, Email auroraxbg@163.com

Purpose: Methotrexate is widely used to treat rheumatoid arthritis; however, the adherence rate greatly varies due to its weekly dosing schedule. Incorrect administration can lead to disease progression and toxicity. To design a graphic-based medication calendar aiming to improve adherence in first-time methotrexate users.

Patients and Methods: This prospective, single-blind, randomized controlled trial included participants aged 18–75 years who were starting methotrexate for the first time or resuming it after a 3-month break. Seventy-nine participants from October 1, 2023, to January 30, 2024, were randomly assigned in a 1:1 ratio to the calendar (38 participants) or control (41 participants) group for 6 weeks and followed up for 2, 6, and 10 weeks. The primary outcome was methotrexate adherence, assessed by the proportion of patients with a PDC value of 100%.

Results: After 6 and 10 weeks, the calendar group had a higher proportion of patients with a PDC value of 100% compared with the control group (97.2% vs 73.2%, $P < 0.004$; 88.9% vs 68.9%, $P < 0.03$, respectively) and a higher correct medication adherence rate within 10 weeks (87.81% vs 69%, $P = 0.0307$). Compared with the control group, the calendar group had a significantly higher rate of on-time return visits during both follow-up visits (97.2% vs 78.0% and 91.7% vs 70.7%, respectively). Additionally, 94.74% of the calendar group patients believed the intervention improved their adherence and wished to continue using it.

Conclusion: The antirheumatic medication calendar improved initial methotrexate adherence; however, its effect diminished following its discontinuation.

Clinical Trial Registration: ChiCTR2300076228 (2023–09-27).

Keywords: antirheumatic medication, controlled clinical trials, medication adherence, methotrexate, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting approximately 1% of the global population. In China, the prevalence of RA is 0.2–0.37%.[1] The main symptoms of RA include pain, joint swelling, and stiffness. Chronic inflammation caused by pathological activation of the immune system gradually destroys the bone, leading to joint deformities and disability.[2] Long-term immune intervention can effectively suppress joint destruction and slow disease progression.

In the 1960s, methotrexate was first used to treat RA and has become the first choice for RA treatment owing to its efficacy, safety, and cost-effectiveness.[3] Methotrexate, a folic acid antagonist, regulates inflammatory cells in synovial membranes, inhibits the production of inflammatory factors, and exerts anti-inflammatory effects through adenosine signaling pathways.[4]

Received: 1 April 2025
Accepted: 4 July 2025
Published: 11 July 2025

However, the effectiveness of methotrexate is often limited by poor patient adherence. The typical methotrexate dose in standard RA treatment is 10–25 mg per week. Low-dose methotrexate guarantees efficacy and safety simultaneously. However, administration at a 1-week interval requires diligent patient adherence. Adherence rates vary between 59% (underuse) and 107% (overuse), and are lower (38%) in China compared to other countries.[5–7] Non-adherence to methotrexate is associated with high disease activity and worse joint function.[8] Additionally, poor adherence, including an overdose of methotrexate, leads to serious adverse reactions and even death.[9]

Fear of adverse reactions and treatment disappointment are the most common reasons for patients to stop taking methotrexate.[10] Therefore, measures to change patients' cognition, such as patient education programs, motivational interview training, psychological intervention, and medical communication, can effectively reduce the occurrence of patients' voluntary discontinuation of medication.[11–13] However, most of the patients who did not stop taking medication had incorrect medication, including reducing the dose, skipping the dose, and even taking an overdose.[14] Incorrect use of methotrexate will increase the frequency and severity of adverse reactions, reduce the therapeutic effect, and undermine patients' trust in the treatment plan. Switching to subcutaneous injection of methotrexate has improved patient adherence,[14] but it is not suitable for all patients with RA. Measures such as using emails, text messages, or phone reminders have a positive effect on the accuracy of patients' medication;[15] however, they are not suitable for older patients who are not proficient in using electronic devices. The picture-based medication calendar can remind patients of the time and dosage of medication intuitively and concisely, and can be viewed and recorded by patients at any time. It is an adherence management tool with great potential. In the field of tumor treatment, medication calendars have been proven to effectively improve medication compliance, meet family care needs, assist medication supervision, and help cultivate the habit of correct medication.[16] However, there are few studies on the design of antirheumatic drug calendars for RA treatment. Additionally, the development of personalized medication calendars remains challenging. There are differences in calendar creation, and a simplified method is needed to create medication calendars. This study aims to develop an antirheumatic drug calendar based on a graphic combination design with an adjustable dose label to achieve personalized adherence reminders and verify its effectiveness in improving methotrexate medication adherence in patients with RA through a prospective randomized controlled clinical trial.

Materials and Methods

Trial Design

The 2010 Consolidated Standards of Reporting Trials guidelines for reporting randomized controlled trials were followed to describe the methods used in this study. To develop an antirheumatic medication calendar and evaluate its effectiveness in improving methotrexate adherence, we conducted a prospective, single-blind, randomized controlled trial. Patient recruitment took place between October 2023 and January 2024 at Ningbo Sixth Hospital, a tertiary orthopedic center renowned for its expertise in orthopedic disease management in eastern Zhejiang, China. Recruitment was continuous without interruption. All recruited patients were administered methotrexate for the first time or had discontinued its use for >3 months to eliminate the influence of prior methotrexate use. The patients were divided into the medication calendar group and the control group. One researcher generated the group number for participants using a randomly generated sequence in Microsoft Excel (Microsoft Corp., Redmond, WA, USA), while another concealed the numbers using masked envelopes. When a patient met the inclusion criteria, the physician opened the envelope on-site to determine the group allocation. The allocation ratio was 1:1. All research data were collated using Microsoft Excel (Microsoft Corp.) and analyzed by another researcher who was blinded to the allocation. Supplementary Figure S1 displays the study flow diagram.

The trial was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Ningbo Sixth Hospital (license number: 2023–06 [X]), and registered in the Chinese Clinical Trial Registry on September 27, 2023 (ChiCTR2300076228).

Eligibility of Participants

The eligibility of patients was confirmed by a rheumatologist and a researcher. Randomization was performed after the patients signed an informed consent form. Patient information was recorded and saved in Microsoft Excel, and it was maintained and updated by a researcher who was blinded to the randomization.

The inclusion criteria were as follows: (i) age >18 years; (ii) adherence to the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria and an RA diagnosis by a rheumatologist;[17] (iii) requirement of methotrexate treatment as determined by a rheumatologist; and (iv) either first-time use of methotrexate or discontinuation of methotrexate for >3 months. The reasons for discontinuation were low compliance and voluntary discontinuation by the patient.

The exclusion criteria were as follows: (i) contraindications to methotrexate or a history of adverse reactions to methotrexate; (ii) inability to understand the medication calendar; (iii) inability to take care of oneself; (iv) having a mental illness or unconsciousness; and (v) refusal to follow-up or sign the informed consent form.

Interventions

The medication calendar in this study was designed by a research team consisting of clinicians, clinical pharmacists, and nursing staff and was adjusted based on the patient's experience and suggestions in the preliminary trial. The medication calendar comprised a calendar and a drug label. It was a monthly calendar with white text on a dark background for weekdays and a blue background for weekends. The date was enlarged, and the lunar calendar was added to make reading easier for older adults. The drug label included the outer packaging, color, and shape of methotrexate tablets, and the number of pills to be taken. Certain areas of the drug label were covered with an ink layer that, when scratched, revealed the words "taken" or "booked". This feature helped reduce patients' errors in medication intake and minimized instances of missed follow-up visits. The calendar and label were mass-produced, matched, and combined according to the doctor's instructions (Figure 1 and Supplementary Figure S2).

Eligible patients were randomly assigned to the medication calendar group or control group in a 1:1 ratio. All patients received drug education from rheumatologists, nurses, and pharmacists before receiving the first dose, including information on usage and dosage, pharmacological effects, adverse reactions, and follow-up requirements. All patients had labels on the outer packaging of the medicine, including usage, dosage, and frequency of use. All patients received their first dose of methotrexate (7.5 mg) for 2 weeks, after which the physician evaluated the patient's condition and adjusted the methotrexate dose for 4 weeks. After 4 weeks, the physician evaluated the patient's condition and adjusted

Figure 1 Calendar design tracking dosages and medication schedules.

https://doi.org/10.2147/PPA.S527173

the methotrexate dose. Patients in the medication calendar group were given a medication calendar matching the dose for 6 weeks, whereas those in the control group were not. Follow-ups were conducted at 2, 6, and 10 weeks to evaluate the impact of the medication calendar on patient adherence (Supplementary Figure S3). When distributing the medication calendar, the researchers demonstrated to the patients how to use it correctly and asked them to explain it again to ensure that they could use it independently. At each follow-up visit, the researchers confirmed whether the patients used the medication calendar correctly. Patients who did not use the calendar correctly or did not use it at all were excluded.

Outcomes

The primary outcome measure was the percentage of patients achieving a proportion of days covered (PDC) value of 100%. The impact of medication calendar use and discontinuation was evaluated at 6 and 10 weeks. The PDC value was calculated as follows: number of days of correct medication within a certain period after the first dose of methotrexate divided by the total number of days. Secondary outcomes included the PDC value, the correct patient adherence rate, the rate of correct medication use at each follow-up time point, the rate of subsequent visits, RA disease activity, and patient satisfaction. RA disease activity was measured using the Disease Activity Score 28 with C-reactive protein (DAS28-CRP). Patient satisfaction was assessed using a 5-point Likert scale based on whether they wanted to continue using the medication calendar. Safety outcomes included adverse reactions to methotrexate. Medication errors were classified into four categories.

"Wrong time:" Taking the correct dose at the wrong time (patients have an inaccurate memory of time).

"Missed medication:" Not taking medication at the correct time (patients have an accurate memory of time).

"Take less medication:" Not taking enough doses at the correct time (patients have an accurate memory of time).

"Take over medication:" Overdose at the correct time (patients have an accurate memory of time).

The patient's medication information was obtained by the attending physician during the follow-up visit. If the patient failed to follow up on time, the information was obtained by telephone.

Sample

A power analysis was performed using the G*Power 3.1.9.7 program (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to determine the sample size with a significance level of 0.05 and a power of 80%. Considering a 10% loss to follow-up rate, the minimum sample size for each group was 36.

Statistical Analysis

Normally distributed data are expressed as means (standard deviations), and differences between the groups were analyzed using independent and paired Student's t-tests. Non-normally distributed data are expressed as medians (IQR) and were analyzed using the Mann–Whitney *U*-test for two-group comparisons. Differences between the two sample rates were analyzed using the chi-square test. According to a previous study,[18] we estimated a mean difference of 20–30% in the proportion of patients with a PDC value of 100% between the two groups. All statistical analyses were conducted using SPSS software (version 26; IBM Corporation, Armonk, NY, USA), and statistical significance was set at $P < 0.05$.

Results

Patients

Of the 79 patients who met the inclusion criteria, 38 were randomly assigned to the medication calendar group and 41 to the control group. Two patients in the medication calendar group were excluded because they did not use the medication calendar as required, resulting in a total of 77 patients. Both groups met the sample size requirements. The male-to-female ratio was 1:2.4 (23 versus [vs] 56), the average age was 51.39 (14.76) years, and the average RA duration was 3.0 (1.00–5.00) years. The patient's disease activity (DAS28-CRP) was 4.52 (0.84). The proportion of farmers was 37.9%. Over 80% of the patients had completed primary education, and > 75% had one or more underlying diseases. Almost all patients received concomitant medications,

Table 1 Characteristics of the Study Population

	Calendar (N = 38)	Control (N = 41)	P-value
Age in years, mean (SD)	52.66 (12.07)	50.22 (16.94)	0.467
Sex, n (%)			0.331
Male	9 (23.7)	14 (34.1)	
Female	29 (76.3)	27 (65.9)	
Occupation, n (%)			0.702
Manual worker	8 (21.1)	12 (29.3)	
Farmer	16 (42.1)	14 (34.1)	
Office worker	9 (23.7)	7 (17.1)	
Freelance worker	1 (2.6)	3 (7.3)	
Unemployed	4 (10.5)	5 (12.2)	
Education level, n (%)			0.410
Never received education	7 (18.4)	7 (17.1)	
Grade school education	15 (39.5)	11 (26.8)	
Secondary education	10 (26.3)	18 (43.9)	
Higher education	6 (15.8)	5 (12.2)	
Duration of rheumatoid arthritis in years, median (IQR)	3.0 (1.00–4.25)	3.0 (1.00–7.50)	0.990
DAS28-CRP, mean (SD)	4.48(0.77)	4.56(0.91)	0.662
Underlying disease, n (%)			0.451
No	10 (26.3)	9 (21.9)	
1 disease	17 (44.7)	15 (36.6)	
2 diseases	7 (18.4)	7 (17.1)	
≥ 3 diseases	4 (10.5)	10 (24.4)	
Concurrent polypharmacy, n (%)			0.841
1 chronic medication	8 (21.5)	9 (22.0)	
2 chronic medications	4 (10.5)	6 (14.6)	
≥ 3 chronic medications	26 (68.4)	26 (63.4)	
Concurrent antirheumatic drugs, n (%)			0.727
No	1 (2.6)	0 (0.0)	
1 medication	13 (34.2)	16 (39.0)	
2 medications	20 (52.6)	20 (48.8)	
≥ 3 medications	4 (10.5)	5 (12.2)	

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range.

including those for other chronic diseases and antirheumatic drugs in addition to methotrexate. No significant differences were observed in the baseline data between the groups (Table 1).

Primary Outcome

The proportion of patients with a PDC value of 100% in the medication calendar group was significantly higher than that in the control group (97.2% vs 73.2%, $P < 0.004$). After discontinuing the medication calendar, the proportion was still significantly higher than that in the control group (88.9% vs 68.9%, $P < 0.03$) but showed a downward trend (Figure 2A).

Secondary Outcome

The correct medication adherence rates within 10 weeks were 87.81% in the medication calendar group and 69.00% in the control group (hazard ratio, 0.343; 95% confidence interval, 0.139–0.851; $P = 0.0307$) (Figure 2B). After 6 weeks, no significant difference was observed in PDC values between the two groups (100.0% [100.0–100.0%] vs 100.0% [95.24–100.0%], $P = 0.217$). However, higher patient distribution was observed in areas with high PDC values on the violin plot in the medication calendar group than in the control group (Figure 2C). Following the discontinuation of the medication calendar, the distribution of patients began to shift toward lower PDC values (Figure 2C). At each follow-up time point, the correct medication adherence rate was significantly higher in the medication calendar group than in the

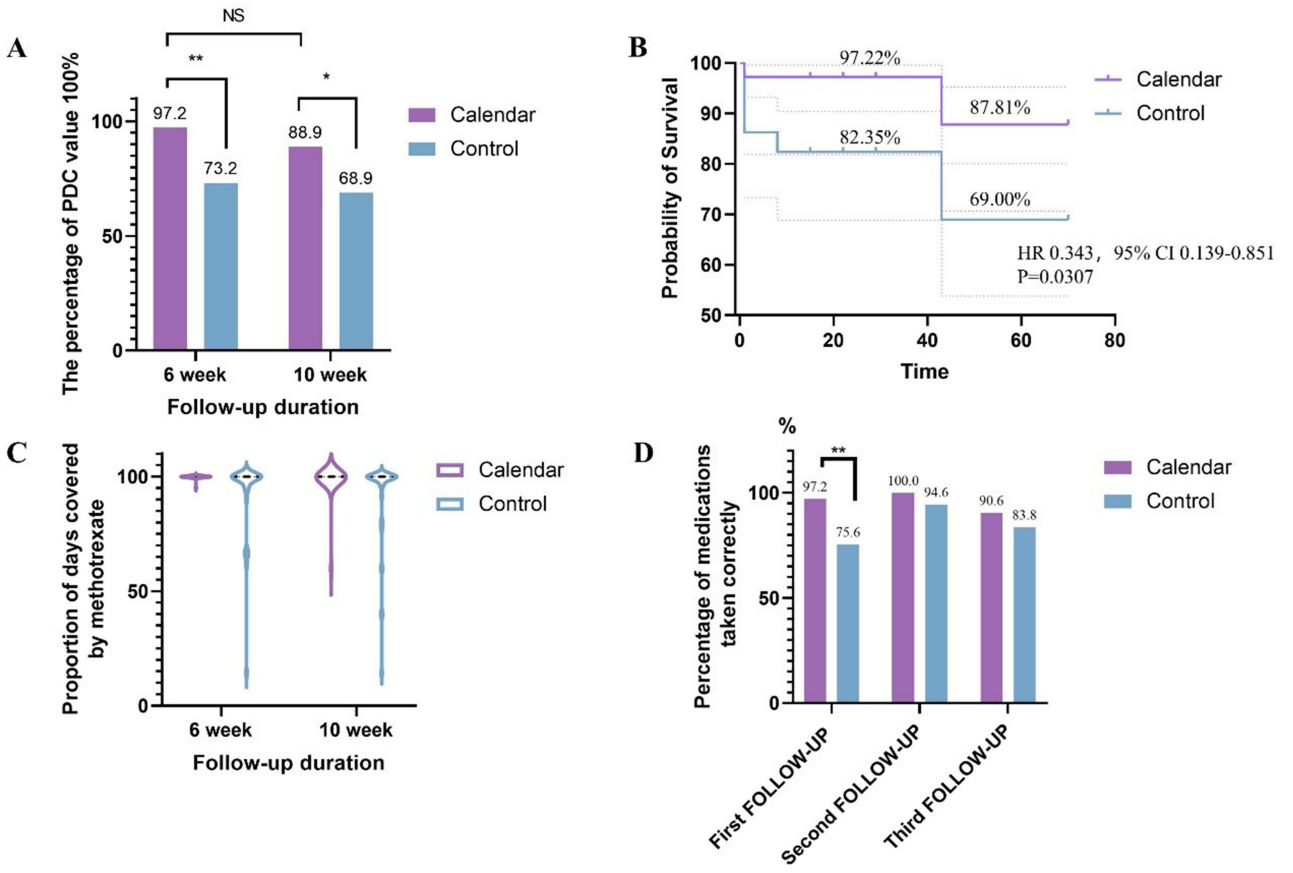

Figure 2 (**A**) The proportion of patients with a PDC value of 100% in the medication calendar and control groups; (**B**) Survival curves using the Log rank test for correct administration of methotrexate; (**C**)Violin plot of the PDC by methotrexate in the medication calendar and control groups; and (**D**) rate of correct medication at each follow-up time point in the medication calendar and control groups. "NS" indicates no statistically significant difference; "*" indicates P < 0.05; "**" indicates P < 0.01. (Created using GraphPad Prism 9.0 and Microsoft Office PowerPoint).
Abbreviations: PDC, proportion of days covered; HR, hazard ratio.

control group (97.2% vs 75.36%, P < 0.007), particularly at week 2 (100.0% vs 80.0%, P < 0.006) (Figure 2D and Supplementary Table 1). At the other follow-up points (6 and 8 weeks), no significant difference was observed in the administration accuracy between the two groups. During the two follow-up visits when doctors adjusted the dosage, the on-time follow-up rate was higher in the medication calendar group than in the control group (97.2% vs 78.0%, P = 0.016; 91.7% vs 70.7%, P < 0.021) (Figure 3A). During the 10-week period, five patients (13.12%) in the medication calendar group and four (9.76%) in the control group, including one (2.43%) who had drug overdose, experienced adverse reactions (Figure 3B). The only medication error in the medication calendar group was a wrong time error. Other error types were observed only after discontinuation of the medication calendar. The distribution of error types in the control group was similar (Figure 3C and D). At each follow-up time point, there was no significant difference in disease activity between the two groups of patients (Figure 4A). However, when the patient's sixth-week data were used as a control, the disease activity of patients in the calendar group still decreased significantly at week 10, while the disease activity of patients in the control group did not decrease (Figure 4B).

Among the 36 participants who used medication calendars, 92.1% believed that the calendar reminded them to take their medications, 94.7% felt it reduced dosage errors, 89.5% found it helpful for scheduling follow-up appointments in advance, 94.7% considered it beneficial for medication management, and 97.3% found it easy to understand. Furthermore, 94.7% of patients in the calendar group believed that the medication calendar improved their adherence and anticipated continued use of the calendar (Figure 4C).

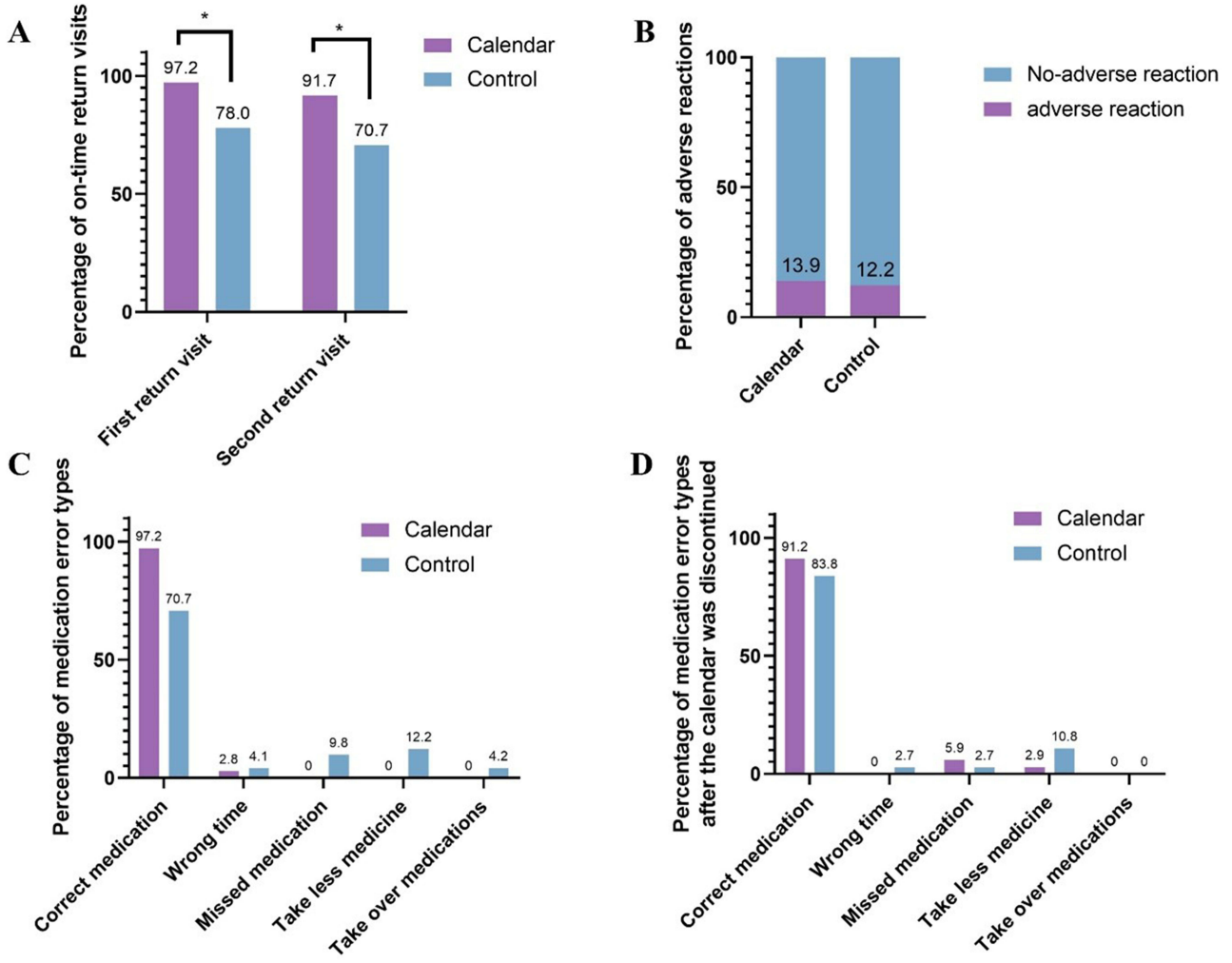

Figure 3 (**A**) The on-time follow-up rate in the medication calendar and control groups; (**B**) incidence of adverse reactions in the medication calendar and control groups; and (**C** and **D**) distribution of different error types in the medication calendar and control groups during periods of medication calendar and withdrawal calendar. "*" indicates $P < 0.05$. (Created using GraphPad Prism 9.0 and Microsoft Office PowerPoint).

Discussion

According to epidemiological data from the Global Burden of Disease (GBD) database, by 2021, the age group with the largest number of RA cases in China is expected to be between 50 and 54 years old, with women accounting for a higher proportion than men.[19] The age and gender distribution of patients with RA included in this study are consistent with the above results. However, it is worth noting that in terms of occupation, there was a higher proportion of farmers among patients. In another study of palindromic rheumatism by the team, patients with RA as controls also showed a higher proportion of farmers (51.5%).[20] Besides the large group of farmers in China itself, the cause of this phenomenon may also be related to the lack of medical resources in the rural areas where farmers live. Farmers often lack an understanding of RA prevention and treatment methods. Humid rural environments and long-term labor may promote the occurrence and progress of RA.[21] Furthermore, only a small number of patients in this study received higher education, which also explains why most patients only started to take methotrexate continuously with at least 1 year of RA. Expanding medical resource coverage in rural areas and RA prevention and treatment missions for low-educated farmers may be one of the keys to reducing the burden of RA disease in China.

In China, the compliance rate of patients with RA ranges from 38.6% to 80.2%. If only the compliance of methotrexate is considered, the compliance rate may be even lower. The main barriers to methotrexate compliance in current studies include adverse reactions and treatment disappointment.[10,22] Patients' concerns about the treatment plan

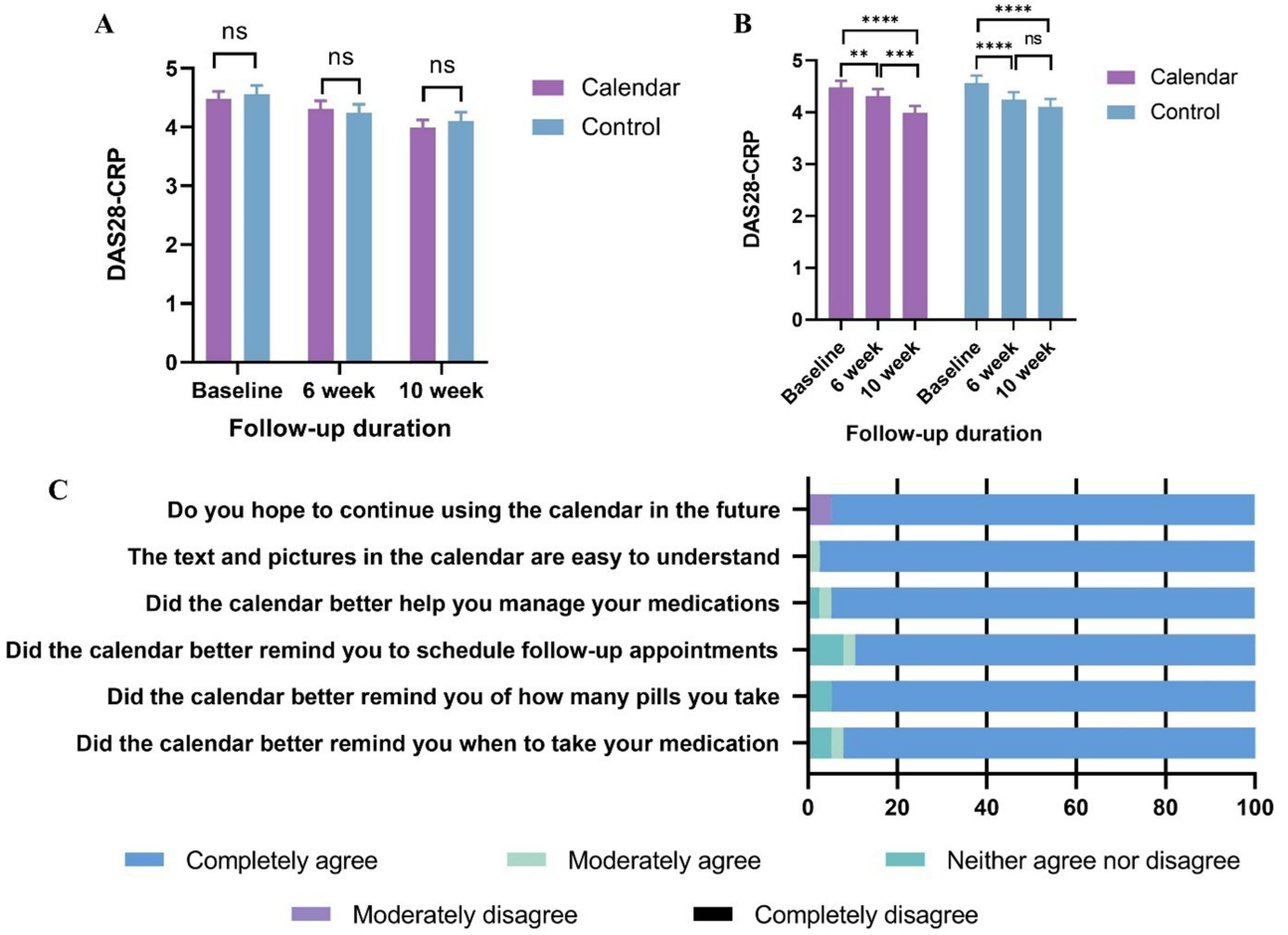

Figure 4 (**A**)The DAS28-CRP was used to measure the disease activity of the patients in the calendar group and the control group; (**B**) The changes in DAS28-CRP over different follow-up duration in the calendar group and the control group (self-control); (**C**) Five-point Likert scale to assess patient satisfaction with the medication calendar. The horizontal axis is the percentage of different answers. "NS" indicates no statistically significant difference; "**" indicates P < 0.01; "***" indicates P < 0.001, "****" indicates P < 0.0001 (Created using GraphPad Prism 9.0 and Microsoft Office PowerPoint).

may lead them to stop taking the drug or actively reduce the dose of methotrexate.[14] Therefore, patient education programs that increase doctor-patient communication, improve patient knowledge, and reduce the fear of adverse reactions to methotrexate can effectively reduce the proportion of patients with RA who actively stop taking the drug.[23–25] However, patients who are willing to take methotrexate face another major barrier to compliance, which is taking the wrong medication. As a "non-daily treatment" (taking the drug only once a week), the phenomenon of missing medication exists in most patients.[14,22] Similarly, in this study, only 75.6% of patients in the control group took methotrexate correctly within 2 weeks after the first visit, indicating that without additional intervention, approximately 25% of patients will use methotrexate incorrectly after discharge. What is more noteworthy is that the proportion of patients who unconsciously take less medication was higher than those who miss it. Incorrect use can lead to poor treatment effects of methotrexate, increased incidence of adverse reactions, and even toxic reactions, which in turn lead to patients' doubts about the treatment plan and fear of adverse reactions, prompting them to stop taking the drug on their initiative. Therefore, how to get patients to take methotrexate correctly is also a key node to improve compliance.

Regular reminders are one of the effective measures to address unintentional non-adherence. Weekly reminder text messages have been shown to have a positive impact on the adherence of patients with RA taking methotrexate.[26] However, some studies have pointed out that reminder text messages have limited effects, and it is difficult to improve the effect of medication reminders alone without the support of medical staff.[23,27] Digital interventions, such as Email reminders or online patient portals, can also effectively improve patient compliance when used as medication

reminders.[28] Unfortunately, in China, the number of people who register for Email accounts and check them regularly is relatively small, especially among older adults. Skilled and active clinical pharmacists can make up for the above limitations,[29–32] but the workload and cost of clinical pharmacists conducting multiple education or follow-up visits for each patient need to be considered, especially in China, where there is a shortage of clinical pharmacists. An effective, easier-to-implement, and less costly medication calendar may be a better choice.

In oncology, caregivers of children with cancer often make mistakes when administering medication in the home setting, including incorrect dosing or frequency and missed doses.[33,34] This is very similar to unintentional non-adherence in methotrexate treatment. An effective medication calendar system can encourage patients to take their medication correctly.[35] However, standardizing the construction of medication calendars is crucial to limiting its clinical application. The printability of medication calendars and the ability to easily adjust medications and doses are of greatest concern.[36] The medication calendar in this study was composed of two components: a calendar and a medication label. Medication labels can be designed to display different medications and doses based on a physician's medication regimen. When obtaining information, patients preferred pictures to text, and graphic-based medication labels were easier to understand.[37,38] An ink layer that could be scraped off by the patient was included to prevent repeated administration of the same medication. The family members of patients in the medication calendar group reported that they used this mark to remind them to take their medications. Once the initial design is completed, the medication calendar can be produced in large quantities without delay and at a low cost.

The proportion of patients with a PDC value of 100% and the rate of correct medication adherence were used to assess the effect of the medication calendar. The proportion of patients with a PDC value of 100% was significantly higher in the medication calendar group compared to the control group, indicating that the medication calendar improved patient adherence. This finding was further confirmed by the correct medication adherence rates. The difference in medication accuracy between the groups was most pronounced during the first 2 weeks; however, the rates improved thereafter, narrowing the difference. This increase was likely attributed to additional medication education provided by doctors and pharmacists during follow-up visits, which had an effect similar to that of the medication calendar. No significant difference in PDC values between the groups was observed during the period of medication calendar usage, potentially due to the insufficient observation period. However, the control group had a higher proportion of patients with low PDC values compared to the medication calendar group.

In the control group, patient medication errors were mainly concentrated in "Take less medication". And "Take over medication", the most dangerous medication error also occurred in one case. This also confirmed that medication calendars reduced the risk and severity of medication errors. Compared with patients in the control group, those in the medication calendar group had significantly higher on-time follow-up rates at both times.

However, the benefits of using the medication calendar waned after discontinuation. The PDC values of patients in the medication calendar group also began to trend toward lower PDC values. Moreover, the proportion of patients with 100% PDC decreased. At 4 weeks after discontinuing the medication calendar, medication adherence in both groups began to decline despite further medication education. Dosage errors were also observed in the medication calendar group. This suggests that the benefits of the medication calendar are based on its continued use; nonetheless, errors might have been observed because the medication calendar was not used for sufficient time to have a lasting effect. In this study, the use of methotrexate resulted in a significant decrease in disease activity for both patient groups compared to the baseline; however, no difference was observed between the two groups. The reason for this phenomenon may be that although the proportion of patients in the control group who took methotrexate correctly was lower than that in the drug calendar group, it still accounted for about 70%. The treatment effect of this part of patients masked the difference in disease activity. Secondly, among patients who took it incorrectly, the main type of error was taking less medication, with no active discontinuation of medication. Therefore, methotrexate can still play a specific therapeutic role, narrowing the treatment gap with patients in the drug calendar group. Additionally, as a drug with a slower onset, the effect of taking methotrexate correctly may require a longer follow-up time to be reflected. When the patient's sixth-week data was used as a control, the disease activity of patients in the calendar group still decreased significantly, while the disease activity of patients in the control group did not decrease significantly. This may be a reflection of the effect of taking methotrexate correctly in the first six weeks. There

was no significant difference in the incidence of adverse reactions between the two groups. However, one patient in the control group developed severe oral ulcers due to daily oral administration of methotrexate. Toxic reactions to drug overdose are more dangerous than other adverse reactions. In the satisfaction assessment conducted at the end of the study, most patients in the medication calendar group felt that the calendar was effective, concise, and easy to use, and they expressed a desire to continue using it in the future.

During the medication calendar usage, regardless of whether there was a medication error, patients and their families used the medication calendar to recall the medication process more accurately. In contrast, patients in the control group had ambiguity/uncertainty in recalling medication use, which was also a cause of errors. The medication calendar appears to be an auxiliary tool for improving the accuracy of adherence assessments. This study did not verify this effect to evaluate related outcomes.

This study had some limitations. First, owing to constraints in funding and personnel, we were unable to recruit a larger number of patients or extend the use of the medication calendar for a longer period. This limitation may have reduced the ability of the medication calendar to help patients develop a consistent habit of taking methotrexate correctly. Second, while the medication calendar helped reduce unintentional medication errors, the study did not include patients with intentionally low adherence—such as those who discontinued medication owing to concerns about side effects or symptom improvement. Third, the medication calendar may increase the likelihood that the patient's relatives will remind or help more accurately, which may also be one of the mechanisms by which the medication calendar works. However, that will lead to an overestimation of the patient's medication adherence. We did not intervene in the behavior of the patient's relatives because this would affect the real-world care mechanism and prevent the patients from seeking support on their own. Since it is impossible to predict which relatives of the patients will assist the patients, this study did not record the educational level of the patient's relatives. Additionally, the inclusion of patients re-initiating methotrexate after >3 months, while necessary for recruitment feasibility, may introduce unmeasured confounding from prior drug exposure. Although dose titration was restarted and historical details were unavailable, subtle biases related to past efficacy/tolerability experiences cannot be fully excluded. In further research, the study scale will be expanded to include more research centers and sample sizes, the recruitment time will be extended, etc. Additionally, different subgroup analyses will be conducted to minimize the interference of patients' relatives or explore the impact of previous methotrexate exposure on outcomes.

Conclusion

The antirheumatic medicine calendar improved drug adherence in patients taking methotrexate for the first time, as recognized by the patients. However, this effect was not sustained after the calendar use was discontinued.

Abbreviations

RA, rheumatoid arthritis; vs, versus; PDC, proportion of days covered; DAS28-CRP, Disease Activity Score 28 with C-reactive protein.

Data Sharing Statement

All relevant data are contained within the article, and the original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics Approval

The trial was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Ningbo Sixth Hospital (license no. 2023-06 [X]), and registered in the Chinese Clinical Trial Registry on September 27, 2023 (ChiCTR2300076228).

Patient Consent

Informed consent was obtained from all patients.

Acknowledgments

We thank all study participants and our hospital colleagues who have been involved in the patients' care and contributed to this research. We would like to thank Editage (www.editage.cn) for English language editing.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Li R, Sun J, Ren LM, et al. Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. *Rheumatology*. 2012;51(4):721–729. doi:10.1093/rheumatology/ker370
2. Kong XY, Wen CP. On research progress of western and Chinese medicine treatment on pre-rheumatoid arthritis. *Chin J Integr Med*. 2019;25 (9):643–647. doi:10.1007/s11655-019-3223-3
3. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheumatic Dis*. 2020;79(6):685–699. doi:10.1136/annrheumdis-2019-216655
4. Zhao Z, Hua Z, Luo X, et al. Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. *Biomed Pharmacothe*. 2022;150:113074. doi:10.1016/j.biopha.2022.113074
5. Xia Y, Yin R, Fu T, et al. Treatment adherence to disease-modifying antirheumatic drugs in Chinese patients with rheumatoid arthritis. *Patient Preference Adherence*. 2016;10:735–742. doi:10.2147/ppa.S98034
6. de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol*. 2003;30(1):44–54.
7. Viller F, Guillemin F, Briançon S, Moum T, Suurmeijer T, van den Heuvel W. Compliance to drug treatment of patients with rheumatoid arthritis: a 3 year longitudinal study. *J Rheumatol*. 1999;26(10):2114–2122.
8. Kang JH, Choi SE, Xu H, Park DJ, Lee JK, Lee SS. Non-adherence to methotrexate was associated with high disease activity and poor health-related outcomes during a 4-year follow-up of rheumatoid arthritis patients. *Clin Experim Rheumatol*. 2022;40(9):1744–1753. doi:10.55563/clinexprheumatol/ir6yds
9. Nimkar SV, Yelne P, Gaidhane SA, Acharya S, Kumar S. Fatal manifestations of methotrexate overdose in case of psoriasis due to dosing error. *Cureus*. 2022;14(10):e30041. doi:10.7759/cureus.30041
10. Heidari P, Cross W, Weller C, Nazarinia M, Crawford K. Medication adherence and cost-related medication non-adherence in patients with rheumatoid arthritis: a cross-sectional study. *Int J Rheumatic Dis*. 2019;22(4):555–566. doi:10.1111/1756-185x.13549
11. Ceranic J, Kisic Tepavcevic D, Petronijevic M, et al. Assessment and prediction of adherence to methotrexate using three self-report questionnaires in patients with rheumatoid arthritis. *Medicina*. 2023;59(8):1446. doi:10.3390/medicina59081446
12. Yielder R, Leibowitz K, Crum AJ, Manley P, Dalbeth N, Petrie KJ. Changing mindsets about methotrexate in the rheumatology clinic to reduce side effects and improve adherence: a randomized controlled trial. *Ann Behav Med*. 2025;59(1). doi:10.1093/abm/kaae089
13. Barton A, Jani M, Bundy C, et al. Translating research into clinical practice: quality improvement to halve non-adherence to methotrexate. *Rheumatology*. 2021;60(1):125–131. doi:10.1093/rheumatology/keaa214
14. Brzezińska O, Kuc A, Kobiałka D, Małecki D, Makowska J. Adherence with methotrexate in Polish patients—Survey research results. *Int J Clin Pract*. 2021;75(3):e13677. doi:10.1111/ijcp.13677
15. Cline A, Unrue EL, Cardwell LA, et al. Internet-based survey intervention improves adherence to methotrexate among psoriasis patients. *J Dermatol Treatm*. 2022;33(6):2784–2789. doi:10.1080/09546634.2022.2071821
16. Tang N, Kovacevic A, Zupanec S, et al. Perceptions of parents of pediatric patients with acute lymphoblastic leukemia on oral chemotherapy administration: a qualitative analysis. *Pediatr Blood Cancer*. 2022;69(1):e29329. doi:10.1002/pbc.29329
17. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology*. 2012;51 Suppl 6:vi5–9. doi:10.1093/rheumatology/kes279
18. Maximos M, Smith K, Harris V, et al. A randomized controlled trial to assess the influence of a picture-based antiemetic medication calendar on medication-taking behavior in adults receiving chemotherapy. *J Oncol Pharm Pract*. 2022;28(8):1763–1770. doi:10.1177/10781552211041680
19. Li Z, Zeng H, Jin B, Zhang M, Zhang X, Chai Y. Trends in rheumatoid arthritis burden in China and globally, 1990-2021: a longitudinal study based on the GBD database. *PLoS One*. 2025;20(5):e0323372. doi:10.1371/journal.pone.0323372
20. Yuan F, Weng Z, Yang Q, et al. Serum miRNA-186-3P and miRNA-382-3P constitute a novel Diagnostic miRNA signature for palindromic rheumatism. *Front Immunol*. 2025;16:1569846. doi:10.3389/fimmu.2025.1569846
21. Tu L, Wei F, Song Y, et al. Development and internal validation of a prediction model for rheumatoid arthritis: a case-control study. *Sci Rep*. 2025;15(1):16620. doi:10.1038/s41598-025-00816-7
22. Sun J, Dai S, Zhang L, Feng Y, Yu X, Zhang Z. Investigating the safety and compliance of using csDMARDs in rheumatoid arthritis treatment through face-to-face interviews: a cross-sectional study in China. *Clin Rheumatol*. 2021;40(5):1789–1798. doi:10.1007/s10067-020-05458-w
23. Mohamed M, El-Maboud A, Salem HF, et al. Predictors of methotrexate adherence and patient's awareness of it in rheumatoid arthritis and its effect on quality of life. *J Pharmaceutical Policy Pract*. 2024;17(1):2365933. doi:10.1080/20523211.2024.2365933
24. Deng W, Hu J. The effects of a pilot intervention for community-dwelling adults with rheumatoid arthritis in Wuhan, China. *Front Public Health*. 2013;1:43. doi:10.3389/fpubh.2013.00043

25. Chen CW, Walter P, Wei JC. Using ChatGPT-like solutions to bridge the communication gap between patients with rheumatoid arthritis and health care professionals. *JMIR Med Educ*. 2024;10:e48989. doi:10.2196/48989
26. Mary A, Boursier A, Desailly Henry I, et al. Mobile phone text messages and effect on treatment adherence in patients taking methotrexate for rheumatoid arthritis: a randomized pilot study. *Arthritis Care Res*. 2019;71(10):1344–1352. doi:10.1002/acr.23750
27. Kini V, Ho PM. Interventions to improve medication adherence: a review. *JAMA*. 2018;320(23):2461–2473. doi:10.1001/jama.2018.19271
28. Yentzer BA, Wood AA, Sagransky MJ, et al. An Internet-based survey and improvement of acne treatment outcomes. *Arch Dermatol*. 2011;147 (10):1223–1224. doi:10.1001/archdermatol.2011.277
29. Ferguson A, Ibrahim FA, Thomas V, et al. Improving medication adherence in rheumatoid arthritis (RA): a pilot study. *Psychol Health Med*. 2015;20(7):781–789. doi:10.1080/13548506.2015.1009917
30. Joplin S, van der Zwan R, Joshua F, Wong PK. Medication adherence in patients with rheumatoid arthritis: the effect of patient education, health literacy, and musculoskeletal ultrasound. *Biomed Res Int*. 2015;2015:150658. doi:10.1155/2015/150658
31. van Heuckelum M, van den Ende CHM, Houterman AEJ, Heemskerk CPM, van Dulmen S, van den Bemt BJF. The effect of electronic monitoring feedback on medication adherence and clinical outcomes: a systematic review. *PLoS One*. 2017;12(10):e0185453. doi:10.1371/journal.pone.0185453
32. Asgari S, Abbasi M, Hamilton K, et al. A theory-based intervention to promote medication adherence in patients with rheumatoid arthritis: a randomized controlled trial. *Clin Rheumatol*. 2021;40(1):101–111. doi:10.1007/s10067-020-05224-y
33. Walsh KE, Dodd KS, Seetharaman K, et al. Medication errors among adults and children with cancer in the outpatient setting. *J Clin Oncol*. 2009;27(6):891–896. doi:10.1200/jco.2008.18.6072
34. Walsh KE, Mazor KM, Roblin D, et al. Multisite parent-centered risk assessment to reduce pediatric oral chemotherapy errors. *J Oncol Pract*. 2013;9(1):e1–7. doi:10.1200/jop.2012.000601
35. Kongshaug N, Skolbekken JA, Faxvaag A, Hofsli E. Cancer patients' perceived value of a smartphone app to enhance the safety of home-based chemotherapy: feasibility study. *JMIR Format Res*. 2021;5(1):e20636. doi:10.2196/20636
36. Mueller EL, Cochrane AR, Carroll AE. Perceptions of chemotherapy calendar creation among US pediatric oncologists. *Pediatr Blood Cancer*. 2023;70(12):e30688. doi:10.1002/pbc.30688
37. Otón T, Carmona L, Andreu JL. Patient's experiences of the barriers and facilitators to Methotrexate. *Musculoskeletal Care*. 2022;20(1):158–166. doi:10.1002/msc.1577
38. Katz MG, Kripalani S, Weiss BD. Use of pictorial aids in medication instructions: a review of the literature. *Am J Health-System Pharm*. 2006;63 (23):2391–2397. doi:10.2146/ajhp060162