Concise report

ImmunoStart: preparing patients for immunosuppression

Charlotte Martin 1, Vinciane Muls2, Céline Brasseur3, Laurent Meric de Bellefon3, Xuan-Lan Lam Hoai4, Jeroen Vanderhilst5, Marc Delforge1 and Silvana Di Romana3

Abstract

Objectives. Patients with immune-mediated inflammatory disease (IMID) present an increased risk of infection. Here, we present the concept of a preventive consultation called ImmunoStart and the first results of its implementation in the care pathway of patients with IMID.

Methods. Relevant information about vaccination history, tuberculosis exposure and other infectious risks were collected through blood sampling, complete anamnesis, chest X-ray and Mantoux test. During the ImmunoStart consultation, vaccination schedules, specific treatments and risk considerations were discussed.

Results. Between October 2016 and February 2020, 437 patients were seen at an ImmunoStart consultation, mainly referred by rheumatologists (56%), dermatologists (25%) and gastroenterologists (18%). A total of 421 (96%) patients needed at least one vaccine (a mean of 3.3 vaccines per patient). Live attenuated vaccine was indicated for 45 patients (10%), requiring them to reduce or interrupt their immunosuppressive drug(s). Ninety-two patients (21%) were treated for latent tuberculosis infection.

Conclusion. This preventive consultation provides a centralized and systematic setting for the direct management of patients with IMID in need of vaccination, treatment of latent disease and specific advice regarding their immunomodulating treatments.

Key words: immune-mediated inflammatory disease, prevention, immunosuppression, vaccination, screening, latent

Key messages

- Screening and vaccinations in patients with immune-mediated inflammatory disease should ideally take place before starting an immunomodulating treatment.
- A centralized setting allows all patients with immune-mediated inflammatory disease to be referred systematically for this complete preventive management.
- A concept such as the ImmunoStart consultation makes it possible to carry out screenings and vaccinations in optimal conditions.

Introduction

Immune-mediated inflammatory diseases (IMIDs) are multifactorial systemic diseases with aberrant immune

Correspondence to: Charlotte Martin, Department of Infectious Diseases, Centre Hospitalier Universitaire (CHU) Saint-Pierre, Rue Haute 922; BE-1000 Brussels, Belgium.
E-mail: charlotte.martin@stpierre-bru.be
responses. Treatment is currently based on conventional synthetic DMARDs (csDMARDs) and, in cases of treatment failure, on biological DMARDs (bsDMARDs), biosimilar DMARDs (bsDMARDs) or targeted synthetic DMARDs (tsDMARDs). Patients with IMID bear an increased risk of infections owing to the immunosuppressive effect of the underlying disease and the use of immunomodulatory medication to treat the IMID. The incidence and severity of infections are higher in patients with IMIDs, including the incidence of vaccine-preventable infections [1–4]. In the last decade, many new b/bs/tsDMARDs have been developed for IMID patients, and an increasing number of indications are being recognized for their use. Moreover, they are used earlier in the course of IMID [5]. International guidelines recommend screening for latent tuberculosis infection (LTBI) before prescription of a TNF-α blocker [6, 7]. Guidelines for vaccination of patients with IMID [5, 6], including recently updated Belgian guidelines [9], are also available, but several reports point out low adherence [10, 11]. The main reasons for low adherence to vaccination are concerns about vaccine safety and lack of clarity about who is in charge of the screening and vaccination of the patient [10].

MTX and CSs, but also abatacept and some TNF-α blockers have shown deleterious effects on the immune response after vaccination with inactivated vaccine, at least for primary vaccination [8, 12]. Live attenuated vaccines are contraindicated during immunosuppressive therapy owing to the risk of disease from the live attenuated pathogen [12, 13]. Finally, latent infections other than Mycobacterium tuberculosis can also reactivate during specific immunomodulating treatments, such as occult hepatitis B [1] or shingles (varicella zoster virus reactivation). Therefore, there is a need for specific screening, for vaccinations and for targeted advice in patients with IMID, ideally before starting an immunomodulating treatment.

Given that it is challenging for IMID specialists to manage this pre-therapeutic assessment together with the disease therapy plan, a joint care programme between IMID specialists (mainly gastroenterologists, rheumatologists, and dermatologists) and infectious disease specialists has been created in our hospital and called the ImmunoStart consultation. ImmunoStart is led by a specialist in infectious diseases, with the aim to ensure a targeted screening, counselling and vaccination programme for each patient with IMID. This consultation is planned as soon as possible after IMID diagnosis. In this paper, we present the data from this innovative ImmunoStart consultation.

Methods

The Centre Hospitalier Universitaire Saint-Pierre (CHU Saint-Pierre) in Brussels is a tertiary public hospital. Specialists in gastroenterology, rheumatology and dermatology of CHU Saint-Pierre created the Biologic Platform, an outpatient clinic welcoming ~200 new patients with IMID per year. Patients are followed-up prospectively, treated with standard of care and/or enrolled in therapeutic clinical trials, and their data are centralized in a database after having signed an informed consent. All adult patients (primarily new patients) are referred to the ImmunoStart consultation as soon as possible even if they are already being treated with an immunomodulating drug. Patients with a flare-up of their disease or patients who have already undergone a vaccinal work-up and already been screened for LTBI are not (immediately) addressed to the consultation. The following serological analyses are performed before the ImmunoStart consultation: hepatitis A, B and C, Treponema pallidum, measles, rubella (women only), varicella, HIV, and sometimes Trypanosoma cruzi and Strongyloides stercoralis if the patient originates from an endemic area. An IFN-γ-release assay is performed. If HBsAg or HBCAb (without HBsAb) is positive, HBV DNA is measured. Chest X-ray (with or without chest CT if X-ray is abnormal) and Mantoux test are performed before the ImmunoStart consultation.

During the ImmunoStart consultation, medical history, former and current treatment, country of birth, travel history and plans, immunization history, tuberculosis contact history and household composition are reviewed with the patient. According to the serological status, and following the recommendations of national and international guidelines [9, 14], the following vaccines can be proposed: diphtheria/tetanus/acellular pertussis combined vaccine (dTap), inactivated polio vaccine, measles/mumps/rubella combined vaccine (MMR), quadrivalent conjugated meningococcal vaccine, B meningococcal vaccine, conjugated and/or polysaccharidic pneumococcal vaccine, quadrivalent inactivated influenza vaccine, hepatitis B vaccine, varicella vaccine, zoster vaccine and papillomavirus vaccine. If the patient has travel plans, hepatitis A vaccine, yellow fever (YF) vaccine, inactivated typhoid vaccine and rabies vaccine can be proposed. If LTBI screening test is positive, treatment is started, and the patient is followed to ensure adherence and tolerance until completion of treatment. Ivermectin 200 μg/kg single dose is administered during the ImmunoStart consultation of patients originating from hyperendemic areas for S. stercoralis, regardless of the serology result. Household vaccination, frequency of gynaecological and/or dental follow-up, specific preventive measures against Listeria monocytogenes, Legionella pneumophila, travel-related diseases or other specific risks are discussed with the patient during consultation.

All patients’ data and administered vaccines and drugs are entered into a specific ImmunoStart database (REDCap Research Electronic Data Capture, v.8.6.0). We used descriptive statistics to summarize the characteristics of our population. Hypothesis tests for differences between groups were performed using non-parametric Wilcoxon–Mann–Whitney and Kruskal–Wallis tests for continuous variables, and Fisher exact tests for our categorical variables. All our P-values are bilateral and considered statistically significant if <0.05. We used SAS statistical software (v.9.4; SAS institute, Cary, NC, USA). The Ethical Committee of CHU Saint-Pierre approved this study (CE/20–07-06).
Results

Between October 2016 and February 2020, 437 patients attended the ImmunoStart consultation (70 in 2017, 193 in 2018, and 162 in 2019). They were mainly referred by rheumatologists (56%), dermatologists (25%) and gastroenterologists (18%) and followed up for RA (23%), cutaneous psoriasis (20%), PsA (18.5%), AS (15%) and Crohn’s disease (13%). Patient characteristics are summarized in Table 1.

Forty-four percent of patients had already started an immunomodulating treatment before attending the ImmunoStart consultation. Two-thirds of the cohort (67%) had travelled or were planning to travel to tropical areas, 62% of whom planned to travel to yellow fever endemic zones.

After checking the serological status and vaccination history, 1380 vaccines were administered to 421 patients (96%) in the context of the ImmunoStart consultation (mean of 3.3 vaccines per patient).

Patients with indication for live attenuated vaccines (measles, varicella and yellow fever)

A total of 140 live attenuated vaccines (43 MMR, 89 YF vaccines and 8 varicella vaccines) were administered during the ImmunoStart consultation: 45 of 437 patients (10%) had to reduce or discontinue their immunosuppressive drugs to allow safe administration of live attenuated vaccines. No side-effects were observed after the administration of these live attenuated vaccines. A total of 55 patients (13%) had negative IgG for measles. Of these, 49% were born in Western Europe. Patients < 45 years old were more likely to need measles vaccine (P = 0.0001). The majority of patients (415 of 437, 95%) were tested positive for varicella zoster virus IgG. Patients planning to travel to yellow fever endemic areas (n = 182) and needing yellow fever vaccine were more likely to be < 45 years old (P < 0.0001) and were less likely to have spent their childhood abroad (P = 0.08).

Patients with indications for inactivated vaccines

During the ImmunoStart consultation, 65% of the patients received a combined diphtheria–tetanus–acellular pertussis vaccine. Patients > 45 years of age and originating from North Africa were more likely to need a tetanus booster (P = 0.035). Fifty (17%) of future travellers to tropical areas had negative hepatitis A IgG. Patients planning to travel to yellow fever endemic areas (n = 182) and needing yellow fever vaccine were more likely to be < 45 years old (P < 0.0001) and were less likely to have spent their childhood abroad (P = 0.08).

Screening for latent tuberculosis infection

Table 2 summarizes the results of LTBI screening in our cohort. At least one of the three LTBI tests was positive in 108 patients (25%). Risk factors for having at least one LTBI-positive test were male sex (P = 0.007), being born or having lived during childhood in Sub-Saharan Africa, Eastern Europe or North Africa (P = 0.0021, 0.0001 and 0.0001, respectively).

Table 1 Summary of the characteristics of the patients attending ImmunoStart consultation (n = 437)

| Characteristic                          | Value        |
|----------------------------------------|--------------|
| Female sex                             | 240 (55)     |
| Age, median (interquartile range), years| 44 (34–55)   |
| Birth region                           |              |
| Western Europe                         | 217 (50)     |
| Eastern Europe                         | 34 (7.8)     |
| North Africa                           | 97 (22)      |
| Sub-Saharan Africa                     | 36 (8)       |
| Central and South America              | 23 (5.2)     |
| Asia                                   | 28 (6.4)     |
| North America                          | 2 (0.5)      |
| Lived > 10 years in another country    | 272 (62)     |
| Lived > 10 years in region             |              |
| Western Europe                         | 43 (16)      |
| East Europe                            | 34 (12.5)    |
| North Africa                           | 94 (34.6)    |
| Sub-Saharan Africa                     | 43 (15.8)    |
| Central and South America              | 24 (8.8)     |
| Asia                                   | 33 (12.1)    |
| North America                          | 2 (0.7)      |
| HIV infection                          | 12 (2.4)     |
| History of close contact with someone diagnosed with tuberculosis | 83 (19) |
| Do not live alone                      | 336 (77)     |

Values are given as n (%) unless stated otherwise.

Table 2 Diagnosis of latent tuberculosis infection (positive Mantoux and/or positive IFN-γ-release assay and/or never-treated tuberculosis sequelae on thoracic CT)

| LTBI test          | Total number | Number positive (% of total cohort) |
|--------------------|--------------|------------------------------------|
| Mantoux            | 383          | 73 (19)                            |
| IFN-γ-release assay| 412          | 59 (14)                            |
| Lung CT            | 53           | 17 (32)                            |
| LTBI diagnosis     | 437          | 108 (25)                           |
| LTBI treatment     | 92           | 2 (21)                             |

Mean skin induration in positive Mantoux tests was 12 mm. LTBI: latent tuberculosis infection.

Table 1 Summary of the characteristics of the patients attending ImmunoStart consultation (n = 437)

| Characteristic                          | Value        |
|----------------------------------------|--------------|
| Female sex                             | 240 (55)     |
| Age, median (interquartile range), years| 44 (34–55)   |
| Birth region                           |              |
| Western Europe                         | 217 (50)     |
| Eastern Europe                         | 34 (7.8)     |
| North Africa                           | 97 (22)      |
| Sub-Saharan Africa                     | 36 (8)       |
| Central and South America              | 23 (5.2)     |
| Asia                                   | 28 (6.4)     |
| North America                          | 2 (0.5)      |
| Lived > 10 years in another country    | 272 (62)     |
| Lived > 10 years in region             |              |
| Western Europe                         | 43 (16)      |
| East Europe                            | 34 (12.5)    |
| North Africa                           | 94 (34.6)    |
| Sub-Saharan Africa                     | 43 (15.8)    |
| Central and South America              | 24 (8.8)     |
| Asia                                   | 33 (12.1)    |
| North America                          | 2 (0.7)      |
| HIV infection                          | 12 (2.4)     |
| History of close contact with someone diagnosed with tuberculosis | 83 (19) |
| Do not live alone                      | 336 (77)     |

Values are given as n (%) unless stated otherwise.

Table 2 Diagnosis of latent tuberculosis infection (positive Mantoux and/or positive IFN-γ-release assay and/or never-treated tuberculosis sequelae on thoracic CT)

| LTBI test          | Total number | Number positive (% of total cohort) |
|--------------------|--------------|------------------------------------|
| Mantoux            | 383          | 73 (19)                            |
| IFN-γ-release assay| 412          | 59 (14)                            |
| Lung CT            | 53           | 17 (32)                            |
| LTBI diagnosis     | 437          | 108 (25)                           |
| LTBI treatment     | 92           | 2 (21)                             |

Mean skin induration in positive Mantoux tests was 12 mm. LTBI: latent tuberculosis infection.
P = 0.0032 and P = 0.0008, respectively) and reporting a close contact with somebody diagnosed with tuberculosis (P = 0.046).

Other screenings
Forty-six patients (10.6%) originated from hyperendemic zones for S. stercoralis, including 36 who were scheduled to receive CSs, who were treated to prevent S. stercoralis reactivation. Four patients (0.9%) were started with hepatitis B reactivation prophylaxis.

Discussion
A large majority (96%) of patients who attended the ImmunoStart consultation needed at least one vaccine. A significant proportion of patients (10%) had to manage a break or reduction in their immunomodulating treatment to receive live attenuated vaccines. Finally, one in every five patients was treated for LTBI. These results stress the high relevance of preventive consultations, such as ImmunoStart, ideally before starting immunosuppression, to facilitate and ensure the quality of future care for IMID patients. CHU Saint-Pierre is a centrally located public hospital in Brussels, accounting for the great diversity in countries of origin of patients. Therefore, in the context of the ImmunoStart consultation, a large number of patients originate from countries endemic for M. tuberculosis, HBV or Strongyloides, for example, highlighting the importance of a robust prevention strategy.

In our experience, 10% of patients had to manage a decrease or a break in their immunomodulating drugs in order to receive a live attenuated vaccine, which could have been avoided if the patient had had a vaccination check-up before starting the immunomodulating drugs. Moreover, the recommendations regarding withdrawal times for immunomodulating drugs, often based on expert opinion rather than on evidence-based or clinical trials, differ greatly from one guideline to another [8, 14]. To address this issue, the recent Belgian guidelines were designed to be as adaptable as possible (based on the half-life of immunomodulating drugs) and make it possible to derive a rule applicable to all drugs, past or future [9]. Nonetheless, administration of live attenuated vaccines is challenging in IMID patients. For example, a contraindication to yellow fever vaccination may hamper the possibility for patients to travel (including to visit their families) to yellow fever endemic areas. Concerning measles-containing vaccine, younger patients born in Western Europe were more likely to test negative for measles IgG. This might be explained by the very low circulation of the measles virus in Western Europe (in Belgium since the 1970s), in contrast to countries outside Western Europe and in developing countries. Outbreaks of measles in Belgium and in several European countries have been observed in recent years [15]. This highly infectious disease can potentially be severe in immunocompromised patients [4]. Moreover, access to post-exposure prophylaxis for measles is complicated and extremely expensive in Belgium. Therefore, it is particularly important to target young patients born in industrialized countries for measles IgG screening before starting immunomodulatory drugs.

Hepatitis A can be severe in immunocompromised patients, and primary vaccination against HAV during administration of immunomodulating drugs has been associated with a high rate of vaccine failure [16]. It is therefore also strongly recommended to check the generation of IgG after vaccination and/or to apply one of the recently described high-dose vaccination regimens [17]. From 2021 onwards, the ImmunoStart consultation has also provided an opportunity to discuss and propose a vaccination schedule against severe acute respiratory syndrome coronavirus 2 that was best suited to each patient.

Given that most IMID patients will benefit from TNF-α blockers at some point in their disease, we performed the same LTBI screening for all patients attending the ImmunoStart consultation. At the ImmunoStart consultation, we diagnosed LTBI according to the either positive strategy [6, 18]. Probably owing to the multicultural nature of our cohort, a high proportion of patients were positive to one of the screening tests. However, this proportion might still be underestimated given the high number of patients already treated with immunosuppressive drugs, which is known to alter the results of LTBI screening [19, 20]. If screening for tuberculosis infection is to be targeted more precisely, it should focus primarily on male patients, those who were born or have lived abroad, or those who report having had close contact with a tuberculosis patient, and preferably, should be carried out before starting immunomodulatory therapy.

Our study has limitations. It should be noted that almost half of the patients of this cohort were already on immunomodulating treatment at the time of the ImmunoStart consultation, and that physicians in some specialties refer patients more systematically than others. Although it is not perfect, the history, the consultation of vaccination records and the serological analyses make it possible to assess the vaccination needs of each patient with reasonable accuracy. To our knowledge, this is the first time that the characteristics of a cohort of patients seen in such a centralized consultation have been reported. Importantly, the ImmunoStart consultation allows infectious disease physicians to acquire expertise in a constantly evolving field and IMID physicians to have a reference infectious disease physician for the management of these complex patients. In conclusion, ImmunoStart consultations provide a centralized and systematic setting for the prevention of infectious complications in patients with IMID.

Acknowledgements
The authors thank Julie Massart, Khadra Massaoudi and Khadija Tarfi for their valuable help in coordinating and caring for ImmunoStart patients, as well as colleagues Christine Ellis, Charlotte De Volder and Thibaut Van Baelen.
for their help in the ImmunoStart consultation. They also thank Emile Freteur for her efficient work and support. C.M. created the ImmunoStart consultation in collaboration with V.M., C.B., L.M.B., X.L. and S.D.R. C.M. is the head of the ImmunoStart clinic. C.M. collected the data and drafted the initial manuscript. V.M., C.B., L.M.B., X.L., S.D.R. and J.V. reviewed and edited the manuscript and provided substantial comments.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

References

1 Chen M-H, Chen M-H, Liu C-Y et al. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis 2017;215:566–73.
2 Lampropoulos CE, Orfanos P, Bournia V-K et al. Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study. Clin Exp Rheumatol 2015;33:216–24.
3 Chiu Y-M, Chen D-Y. Infection risk in patients undergoing treatment for inflammatory arthritis: non-biologics versus biologics. Expert Rev Clin Immunol 2020;16:207–28.
4 Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA 1992;267:1237–41.
5 Furer V, Rondaan C, Heijstek MW et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39–52.
6 Belgian guidelines on the diagnosis and management of latent tuberculosis infection. FARES asbl. https://www.fares.be/tuberculose/publications/recommendations/belgian-guidelines-on-the-diagnosis-and-management-of-latent-tuberculosis-infection (15 June 2021, date last accessed).
7 Goëb V, Ardizzone M, Arnaud L et al. Conseils d’utilisation des traitements anti-TNF et recommandations nationales de bonne pratique labellisées par la Haute Autorité de santé française. Rev Rhum oct 2013;80:459–66.
8 Bühler S, Eperon G, Ribi C et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly 2015;145:w14159.
9 20191014_shc_9158_ic_and_vaccination_vweb.pdf. https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20191014_shc_9158_ic_and_vaccination_vweb.pdf (15 June 2021, date last accessed).
10 Malhi G, Rumman A, Thanabalan R et al. Vaccination in inflammatory bowel disease patients: attitudes, knowledge, and uptake. J Crohns Colitis 2015;9:439–44.
11 Wasan SK, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. Inflamm Bowel Dis 2011;17:2536–40.
12 Visser LG. TNF-α antagonists and immunization. Curr Infect Dis Rep 2011;13:243–7.
13 Shearer WT, Fleisher TA, Buckley RH et al.; Medical Advisory Committee of the Immune Deficiency Foundation. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol 2014;133:961–6.
14 Furer V, Rondaan C, Heijstek MW et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39–52.
15 Leong WY. Measles cases hit record high in Europe in 2018. J Travel Med 2018;25:1–2. https://academic.oup.com/jtm/article/doi/10.1093/jtm/tay080/5089986
16 Garcia Garrido HM, Wieten RW, Grobusch MP, Goorhuis A. Response to hepatitis A vaccination in immunocompromised travelers. J Infect Dis 2015;212:378–85.
17 Rosdahl A, Herzog C, Frösner G et al. An extra priming dose of hepatitis A vaccine to adult patients with rheumatoid arthritis and drug induced immunosuppression – a prospective, open-label, multi-center study. Travel Med Infect Dis 2018;21:43–50.
18 Jung YJ, Lee JY, Jo K-W et al. The ‘either test positive’ strategy for latent tumour necrosis factor treatment. Int J Tuberc Lung Dis 2014;18:428–34.
19 Jauregui-Amezaga A, Turon F, Ordás I et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. J Crohns Colitis 2013;7:208–12.
20 Béland E, Semb S, Ruhwald M et al. Prednisolone treatment affects the performance of the QuantIFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. Inflamm Bowel Dis 2011;17:2340–9.